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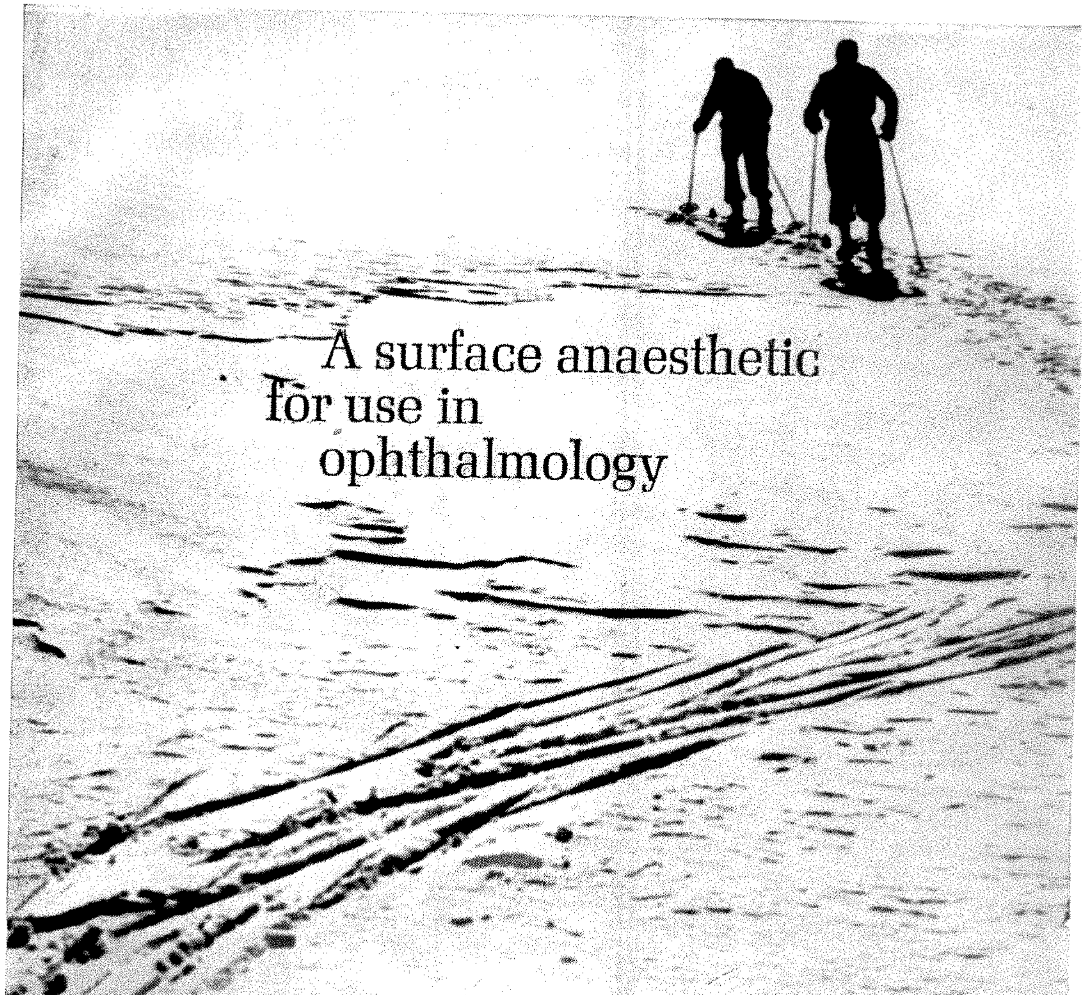

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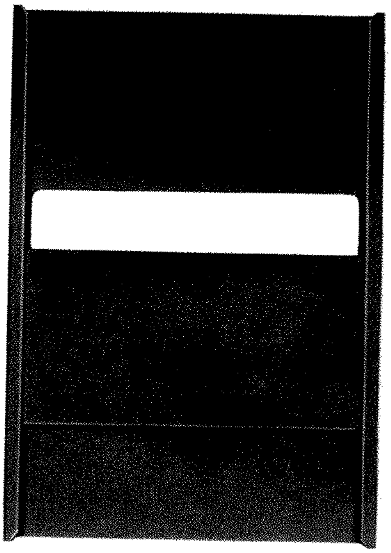

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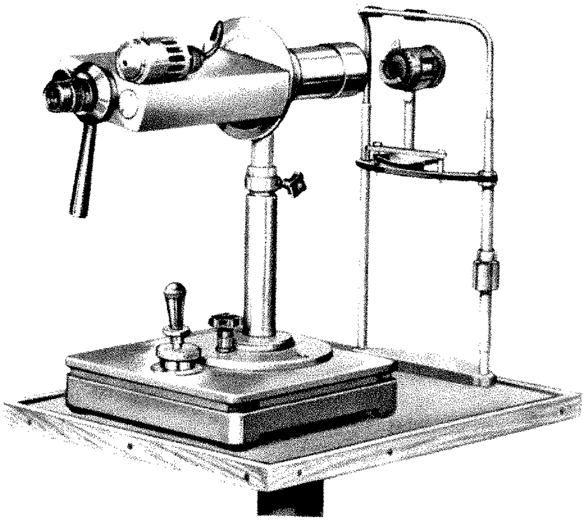

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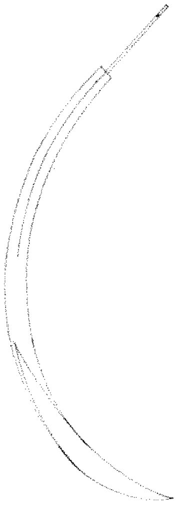

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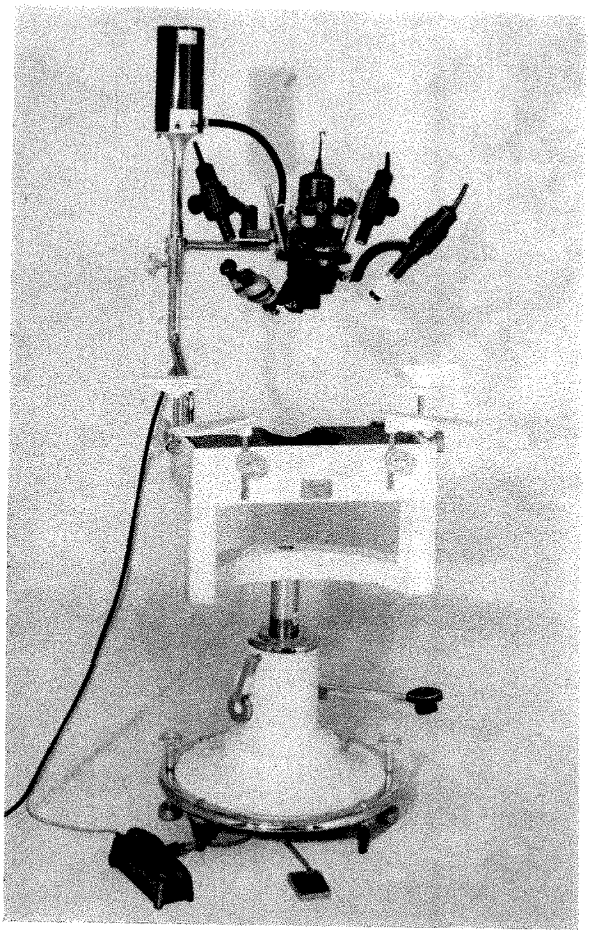

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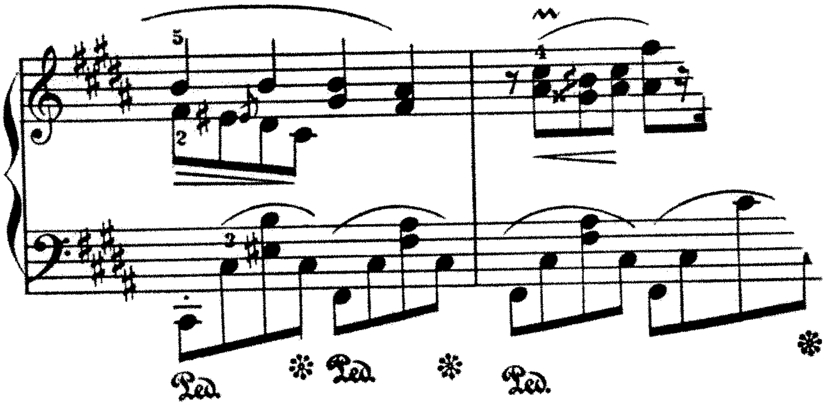

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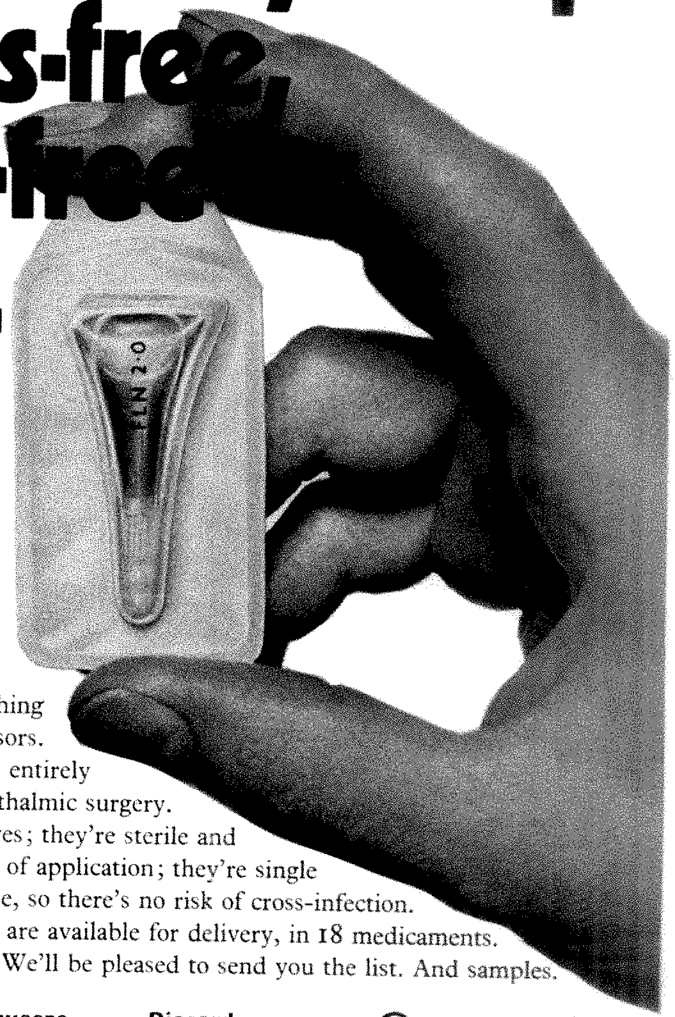

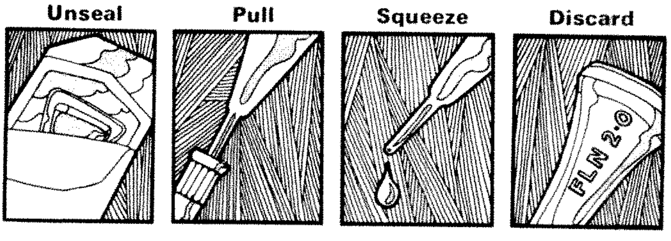

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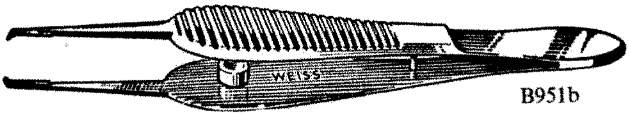

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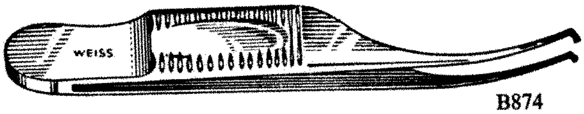

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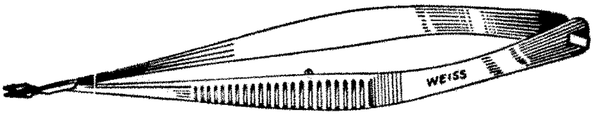

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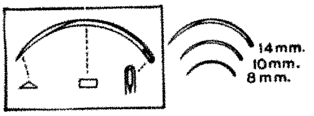

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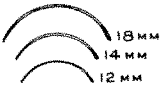

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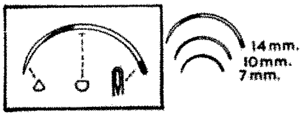

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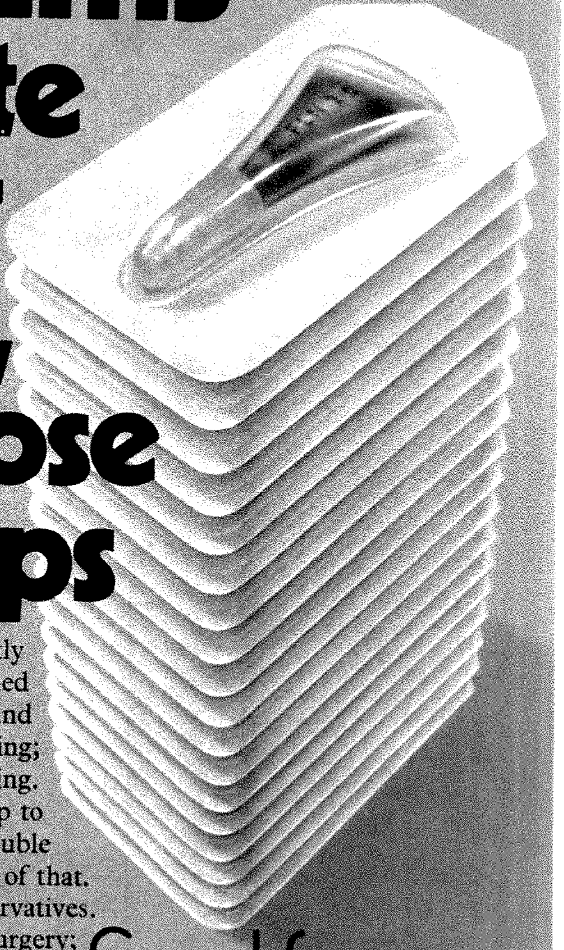

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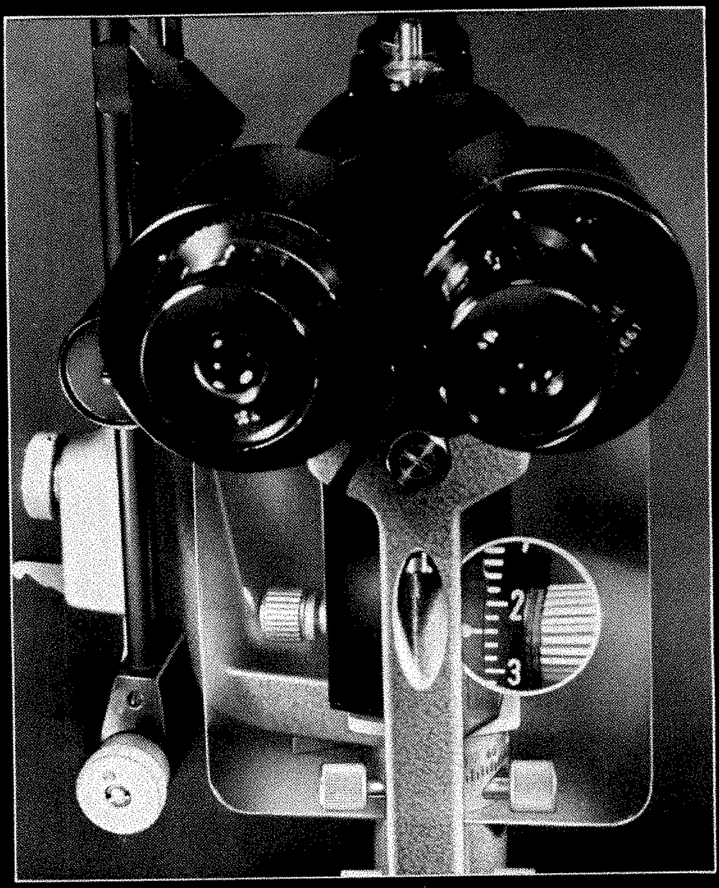

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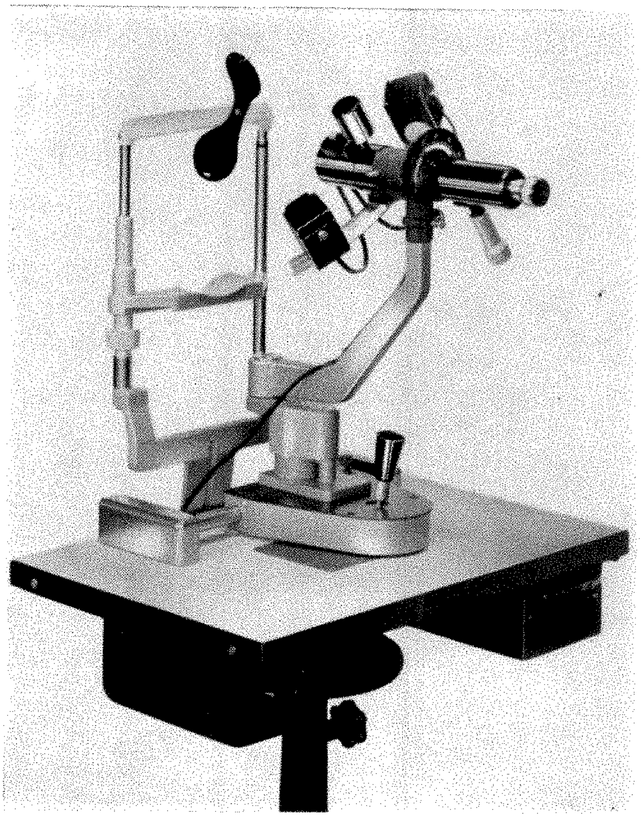

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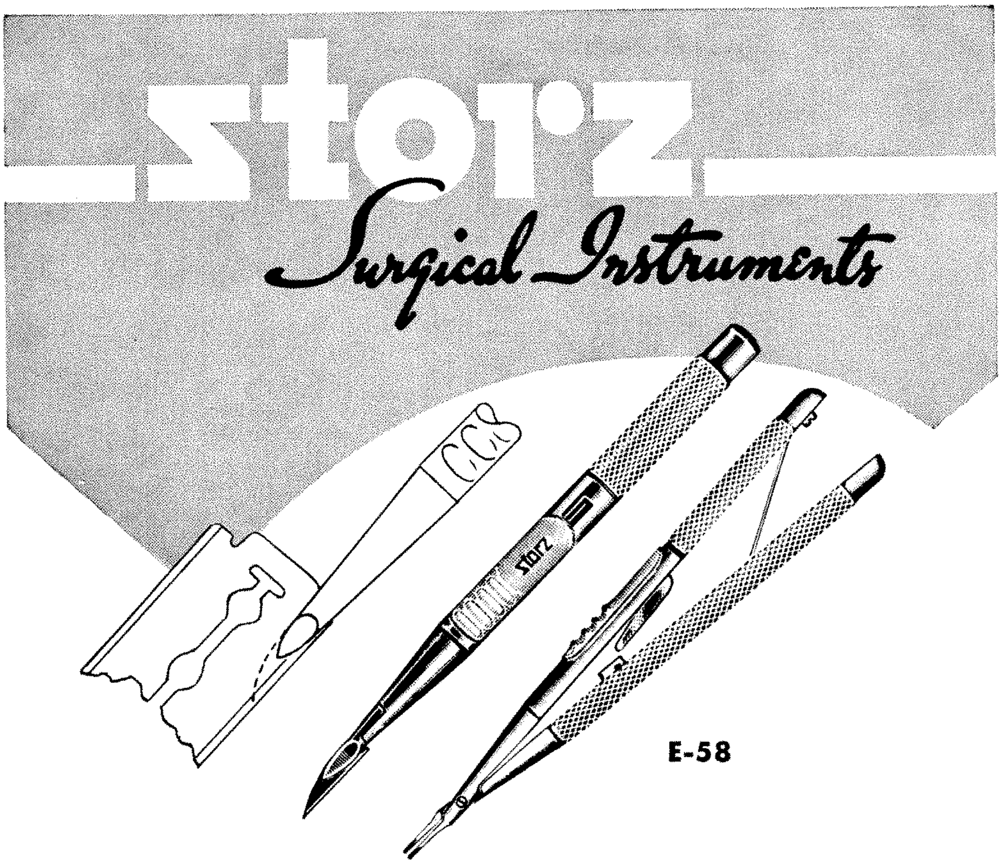

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Communications

Simple diabetic retinopathy

Evolution of the lesions and therapeutic considerations

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The name Simple (or Exudative) Diabetic Retinopathy includes a variety of diabetic changes, in particular, lipoid exudates, microaneurysms, and haemorrhages. The term specifically excludes cases in which new vessel formations are present: Proliferative or Malignant Diabetic Retinopathy (Burditt, Caird, and Draper, 1968). Simple diabetic retinopathy shows a marked tendency to be symmetrical and to involve the posterior poles of the eyes; for this reason the term Diabetic Maculopathy is sometimes applied. The lipoid exudates constitute the most obvious clinical sign, but the more fundamental lesions are small islets of pathological capillaries in which microaneurysms are the most easily observed elements. These changes in the minute vessels usually precede the lipoid changes and it is the deposition of lipoid and oedematous changes in the macular area which cause the risk of the loss of central vision. The present investigation has two aims in view:

(1) To examine the spontaneous changes in exudates and foci of capillary damage which take place over a period of several years, for only by a knowledge of these changes can the effect of therapy be assessed.

(2) To determine if capillary lesions in any particular anatomical areas could be shown to have a particularly adverse effect in the formation of exudates or oedema in the macular area.

This investigation has been made retrospectively by the examination of serial fundus photographs taken over several years of patients suffering from bilateral simple diabetic retinopathy of varying degrees of severity.

Clinical material

Fifty eyes of 25 patients have been selected and studied by serial fundus photographs for periods of between 2 and 7 years. The average time of observation of each eye is 3·6 years and the interval between successive photographs rather less than 6 months. The general data (age, sex, duration of diabetes, etc.) are given in Table I and the details of the photographic observations in Table II. In order to confine the observations to the retinal changes, only eyes with clear media were included in this study. Some of the patients were included in a previous study as cases or controls in an investigation of the effects of a corn-oil diet (King, Dobree, Kok, Foulds, and Dangerfield, 1963).

Ophthalmoscopic and other examinations were made at each visit of the patient, but the photographs form the basis of the data obtained. Although the resolution of the fundus camera is greatly inferior to that of the human eye, a permanent record which can be examined and re-examined and any lesion traced forwards or backwards in time is superior to purely visual records and is less liable to observer error.

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Methods of examination

At the initial examination or early in the series most of the posterior half of each fundus was photographed by the Zeiss fundus camera to cover the following seven fields:

(*a*) The disc as centre.

(*b*) The four main groups of vessels for about 25° beyond the disc.

(*c*) The disc and macula.

(*d*) The macula as centre.

Subsequent routine pictures always included the posterior pole, that is within the area bounded by the superior and inferior temporal vessels above and below with the disc medially and an area of retina about 2 disc diameters lateral to the disc, and any other areas in which pathological changes were taking place.

The number of slides taken of each patient is considerable, ranging from 35 (Case 23) to 162 (Case 4), so that it is relatively easy to secure identical fields for comparison throughout any given series.

Comparison of serial slides was made directly in all cases. An additional technique which provided valuable data was to trace the lesions from a retro-illuminated screen on to transparent polythene sheets. It was possible by this means to establish the permanence of small groupings of capillary changes over long periods and at the same time to record the waxing and waning of the lipoid deposits. This technique was used in 27 eyes (54 per cent. of the series), see Figs 1*a* and 1*b* (opposite).

Table I *Sex and age of 25 patients studied*

Case no.	*Sex*	*Age (yrs)*	
		At start of trial	*At onset of diabetes*
1	M	64	48
2	M	60	43
3	F	61	50
4	F	42	20
5	F	54	51
6	F	67	48
7	F	66	63
8	F	61	57
9	M	56	49
10	M	69	?
11	F	64	62
12	F	57	57
13	F	59	43
14	M	51	51
15	M	52	49
16	F	66	?
17	F	68	52
18	F	53	43
19	F	60	56
20	F	64	55
21	M	57	49
22	F	67	55
23	M	51	31
24	M	49	29
25	M	48	27

Findings

(I) Foci of pathological capillaries (Table II, overleaf)

(*i*) *Appearance*

Microangiopathy in simple diabetic retinopathy occurs as small scattered foci lying mainly at the posterior pole. These areas are most easily identified ophthalmoscopically by small clusters of microaneurysms, but varicosed capillaries and small punctate haemorrhages also enter the picture (Ashton, 1949), so that the foci appear on the photographs as collections of small red dots, the largest covering an area up to one-eighth of the area of the disc in extent (Figs 1*a* and 1*b*). Depending on the leakage from the damaged capillaries, a varying amount of oedema is also present.

(*ii*) *Numbers of foci per fundus* (Table II)

The foci varied in number from 0 (3 cases) to 8 (average 2·8) per eye. No focus was accepted unless it appeared in at least two successive photographs and care was taken to identify some of the smaller aneurysmal clusters by serial tracings (see method above). It must be clearly understood that only the larger foci of capillary damage can be identified by colour fundus photographs, so that these figures could easily be doubled if all those observable by ophthalmoscopy were included.

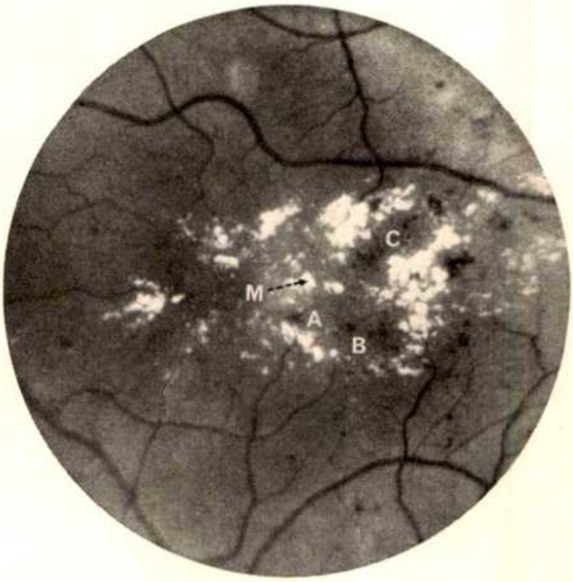

FIG. 1a *Photograph of left fundus on May* 11, 1965, *showing foci of pathological capillaries* (*A*, *B*, *C*) *and surrounding exudates*

M = Macula

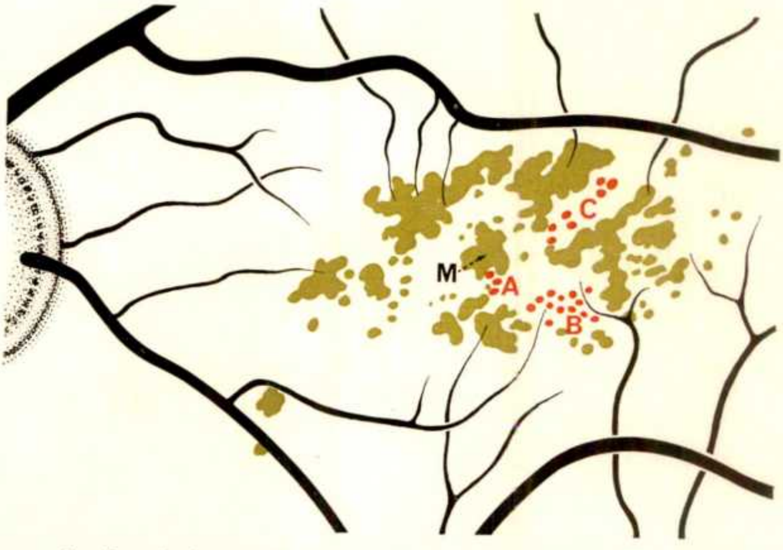

FIG. 1b *Same fundus as in Fig.* 1a, *showing the effect of superimposing four photographs taken between January* 14, 1964, *and May* 3, 1966. *The green areas indicate the total area of retina in which lipoid exudate has occurred during this period. The foci A, B, C of Fig.* 1a *appear in each photograph and these foci remain free from lipoid deposits*

(*iii*) *Duration of foci* (Table II)

The length of time that groups of pathological capillaries could be identified is given in Table II, which indicates the longest time for which any one focus could be traced. Some foci proved to be remarkably stable and in ten eyes were visible in successive photographs for 4 years and upwards.

(*iv*) *Location of foci of pathological capillaries*

A striking feature of the distribution of the foci was the large number which was found in a

P. 25,371

Table II *Ocular data in 25 patients*

Case no.	*Eye*	*Observation*		*Visual acuity*		*Pathological capillary foci*			*Size of macular plaques (in disc areas)*
		Duration (yrs)	*Number*	*Initial*	*Final*	*Number*	*Duration (yrs)*	*Position of paramacular foci (in disc diameters from centre)*	
1	R	2·2	3	6/18	6/60	4	2·2	lat. 1·0	0·5
	L	2·2	4	6/18	6/24	4	2·2	lat. 0·5	0·25
2	R	3·4	8	Counting fingers	3/60	—	—	—	2·5
	L	3·4	11	Counting fingers	6/60	4	1·5	sup.-med. 0·5	0·25
3	R	5·0	6	6/24	6/60	1	1·5	—	0·25
	L	6·7	7	6/24	5/60	2	6	lat. 1·0	2·0
4	R	7·0	12	6/9	6/9	2	5	lat. 1·0	0·125
	L	7·0	10	6/60	6/9	1	5	lat. 1·0	0·5
5	R	4·1	6	6/9	6/24	1	1+	lat. 1·0	0·125
	L	4·1	6	6/60	6/60	3	1+	lat. 0·5	0·5
6	R	2·5	5	6/24	6/24	6	2·5	inf. 0·25	—
	L	2·5	5	6/18	6/24	4	2·5	inf.-lat. 1·0	0·05
7	R	2·3	6	6/9	6/18	3	1	lat. 1·0	0·5
	L	2·3	7	6/12	6/60	2	1·7	lat. 0·5	0·25
8	R	3·3	7	2/60	2/60	—	—	—	0·5
	L	3·9	8	6/18	6/18	3	4	(1) lat. 1·0 (2) lat. 0·5	
9	R	5·3	7	6/60	Hand movements	1	1·3	Inside plaque	2·0
	L	5·1	8	6/60	6/60	2	4·9	(1) sup. 1·0 (2) lat. 1·0	1·25
10	R	2·3	5	6/12	6/24	3	1·3	inf. lat. 0·5	—
	L	2·3	4	6/60	6/60	2	1·3	—	—
11	R	2·5	8	6/9	6/9	2	2	—	—
	L	2·5	6	6/24	6/60	3	4·3	(1) lat. 0·5 (2) inf. 0·75	—
12	R	3·9	7	3/60	6/24	6	3·7	(1) sup.-lat. 1·0 (2) lat. 1·0	1·0
	L	3·9	6	6/9	6/36	6	2·3	(1) lat. 0·5 (2) lat. 1·0	0·5
13	R	3·3	7	6/6	6/9	2	3·3	(1) lat. 0·25 (2) lat. 1·5	0·1
	L	3·8	10	6/6	6/6	3	2·3	inf.-lat. 0·25	0·2
14	R	2·0	6	6/9	6/6	3	2	—	—
	L	2·0	6	6/5	6/5	2	1·3	sup.-lat. 0·25	0·05
15	R	5·5	10	6/18	6/9	2	1·8	lat. 0·75	0·1
	L	4·5	13	6/6	6/9	4	4·3	lat. 1·0	0·2
16	R	4·4	11	6/36	6/36	8	4·4	(1) inf. 0·5 (2) lat. 1·50	1·5
	L	4·4	7	6/24	6/24	2	2·2	inf.-lat. 0·5	0·125
17	R	2·1	8	6/24	3/60	3	2·0	(1) lat. 0·50 (2) lat. 1·0	—
	L	2·1	9	6·24	6/24	3	2·0	lat. 1·0	—
18	R	4·7	8	6/9	6/24	3	4·0	lat. 1·0	—
	L	4·3	6	6/60	6/60	—	—	—	0·25
19	R	3·0	9	3/60	6/36	3	0·8	lat. 1·0	0·50
	L	3·0	10	Counting fingers	Counting fingers	2	1·0	lat. 1·0	4·0
20	R	3·5	8	6/60	6/60	2	3·7	(1) sup.-lat. 0·25 (2) inf.-lat. 0·25	0·125
	L	3·5	8	6/24	6/18	3	3·1	—	0·25
21	R	2·7	6	6/9	6/6	4	2·7	(1) lat. 0·5 (2) lat. 1·0	—
	L	2·7	7	6/6	6/6	2	1·4	inf. 0·5	—
22	R	4·1	11	6/60	6/36	3	4·0	(1) lat. 1·0 (2) med. 0·25	0·75
	L	3·5	12	6/36	6/36	5	0·8	lat. 0·25	0·25
23	R	2·0	7	6/6	6/6	1	2·0	lat. 1·0	—
	L	2·0	5	6/6	6/9	1	2·0	sup.-lat. 1·0	—
24	R	3·8	8	6/6	6/6	3	3·7	lat. 1·0	0·125
	L	4·3	11	6/6	6/9	4	3·8	lat. 0·50	0·125
25	R	6·7	11	6/12	6/9	6	6·4	inf.-lat. 1·50	—
	L	6·7	8	6/9	6/6	1	6·4	inf. 0·25	—

(1) Visual acuities taken to lowest correct line on Snellen chart
* Foci of pathological capillaries measured from centre of macula within a radius of 1·5 disc diameters

small area lateral to the macula. Out of a total of 140 foci, 44 (31·4 per cent.) lay on the lateral side of the macula (including the supero- and infero-temporal positions) and within 1½ disc diameters of it.

This concentration of microaneurysmal clusters and varicosed capillaries in this small area lateral to the macula is thought to be connected with the anatomical distribution of the vessels; for, in the region lateral to the macula, there is a confluence of small arterioles and venules from the main superior and inferior temporal vessels and these small twigs have vascular territories which interdigitate across the horizontal raphe of the retina (Fig. 2). In contrast, medial to the macula and above and below it, the small vessels run radially towards the parafoveal zone.

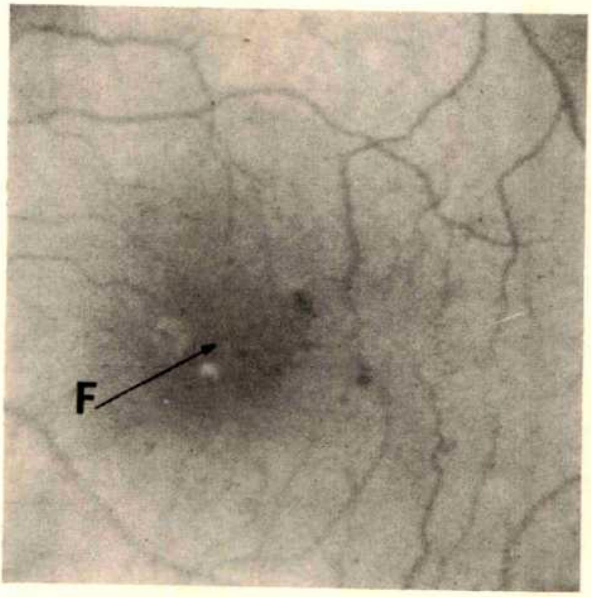

FIG. 2 *Vessels surrounding the macula of the left eye. Note the confluence of vascular territories across the horizontal raphe lateral to the macula. Note focus of pathological capillaries just lateral to macula*

F = Fovea

Apart from the lateral macular congregation, pathological capillary foci are fairly widely scattered over the posterior fundus. They are noticeably away from the main vascular trunks. This distribution is interesting in connexion with another investigation currently reported (Taylor and Dobree, 1970), in which we have studied the location of new vessel formations from similar photographic records of patients with proliferative diabetic retinopathy. In this group the new vessel formations which were of sufficient size to be seen on fundus photographs were almost entirely confined to the area of the disc and main vascular branchings.

(II) Lipoid exudates

(1) FORM OF EXUDATES

In a previous paper (King and others, 1963), three forms of lipoid deposit were described:

(*a*) clusters of small flecks of lipoid material.

(*b*) deposits in the form of large and small rings.

(*c*) plaques of lipoid material at the posterior pole often involving the macula.

The present survey has confirmed the previous findings and added new information on the relationship of exudates to the foci of pathological capillaries.

(*a*) *Features of cluster forms*

Small fleck-like deposits of lipoid are arranged in small clusters up to one disc area in extent. There is often evidence of preceding capillary pathology in the vicinity. These are the most transitory forms of exudate and often appear and disappear in as short a time as 4 months.

(*b*) *Features of ring forms*

Ring exudates exist in all sizes from about one-sixth of a disc area to large wreath-like aggregations several disc diameters across. For the purpose of this paper small rings are defined as those having an outer limit less than one disc area and large rings as those of one disc area or more.

The number of ring forms found was considerable; 93 small rings (average 1·9 per fundus) and 27 large rings (average 0·54 per fundus) were identified.

Serial observations and especially tracings often reveal unsuspected ring forms, for if an arc of a ring is present on one slide the observations before and after frequently supply further arcs to complete the ring.

The general pattern of the formation of rings, which appears to be the fundamental form of lipoid deposit, is that of a continuous process of deposition and re-absorption so that any one slide may show several rings in varying stages of development. The duration of the rings is variable and depends largely on the amount of lipoid originally laid down. The smallest rings may appear and disappear within 6 months and those about the size of a disc take 2 to 3 years to form and disappear. The largest wreath-like rings are especially stable and in two eyes were found to persist for over 4 years.

Houston and Wise (1957) noted that numerous ring forms contained a central cluster of microaneurysms. This survey supports their observations. Out of 93 small rings, 61 (65·6 per cent.) had aneurysms or other evidence of pathological capillaries situated in their central areas. With regard to the 27 large rings, fifteen (55·5 per cent.) had areas of capillary pathology included, several foci being present inside some of the larger rings.

(*c*) *Lipoid plaques at posterior pole*

In 35 out of the fifty eyes examined (70 per cent. of cases) plaque-like lipoid deposits either covered or involved the macular area. These varied in size from massive confluent deposits some 2 to 3 disc diameters across to small aggregations about one-tenth of a disc area in extent. They were sometimes rounded masses centred at the macula or arranged in a somewhat stellate form consisting of a number of smaller deposits. An attempt has been made to record their greatest extent in terms of disc area (Table II). Their duration depends largely on the mass of lipoid material involved and the largest persist for over 5 years. Without exception the plaques varied in size throughout the period of observation, and in twenty out of the 35 cases periods of both increase and decrease were noted.

A macular deposit is often part of a ring formation (Welsh, 1968) and often forms the largest deposit of that ring. This was found in nine (18 per cent.) of the eyes. Deposition of lipoid in the macular area is probably related to the fact that the macular and paramacular tissues readily imbibe fluids in many pathological conditions and there appears to be a preferential "pooling" of lipoid here. It was not possible to make out any close association between foci of capillary pathology and macular plaques because of the frequency of foci in the paramacular area. Thus, out of the 35 eyes showing macular deposits, 27 (77·1 per cent.) had one or more foci within 1 disc diameter of the macula, and of the fifteen eyes without deposits thirteen (86·7 per cent.) had similar foci. On the other hand it must be remembered that the period of observation (average 3·6 years) represents only a fraction of the time of duration of the retinopathy.

(2) LATE MACULAR CHANGES

Deposits of cholesterol crystals were left as residues after large macular plaques in two eyes (4 per cent.). A marked macular pigmentation following resolution of a plaque was seen in six eyes (12 per cent.) and a connective tissue scar in a further case. These findings emphasize once again an important observation in our previous study (King and others, 1963), namely, that even after complete absorption of a macular plaque, permanent damage to the macular tissues is usual.

(3) APPEARANCE AND DISAPPEARANCE OF LIPOID DEPOSITS

It has long been known that there is a continuous process of deposition and absorption of lipoid material in a diabetic fundus, but the full extent of this was not recognized until tracings of the lipoid deposits were superimposed one over the other and the total area of retina involved was charted (Figs 1*a* and 1*b* show an example, but this is by no means the most extensive deposition in the series). The foci of pathological capillaries were also charted and these areas remained free from lipoid while the tissue surrounding them became heavily infiltrated by deposits either in the form of rings or as more isolated masses. Examination of the edge of an area of lipoid deposition either in the macula or elsewhere usually provided information whether lipoid was being laid down or absorbed. In the former case the contours are rounded (map of Africa appearance) and in a regressive phase there are extensive "bays", "inlets" and "off-shore islands" (map of N. America appearance).

(4) MACULAR OEDEMA

Oedema of the macula was a common finding throughout the series. In the case of the larger lipoid deposits on and around the macula, oedema is especially marked in the early stages of their formation. Fundus contact lens examination in these cases reveals that the retina may be swollen to two or three times its normal thickness. Macular oedema of all degrees may be found with or without lipoid deposits and in one case cyst formation occurred. The fluorescein studies of Gass (1968) in exudative retinopathy are particularly illuminating in this connexion. He has demonstrated that in these cases the vascular leakage is largely confined to the paramacular region on the temporal side of the macula.

(5) RELATION OF MACULAR CHANGES TO VISUAL ACUITY

There is a broad correlation between the size of a macular deposit at its greatest development and the loss of central vision. Fourteen of the fifty eyes had macular lipoid deposits of half a disc area or greater. These are shown in Table III (overleaf). It will be seen that in six eyes with a macular plaque greater than one disc area the best vision was 6/36 and in the remaining five eyes the best vision was 6/60 or below. Of the eight eyes with a plaque between half and 1 disc area in extent, one eye achieved 6/9 vision and the remainder between 6/18 and 6/60.

Seven of the fourteen eyes showed a complete or almost complete clearing of lipoid in the macular and paramacular area. Four of these eyes showed a marginal improvement in the greatly reduced vision, one deteriorated, and two were unchanged. This failure to recover vision after the absorption of macular lipoid thus occurs in cases of spontaneous clearance and in cases in which the disappearance of lipoid is associated with treatment by corn-oil (King and others, 1963) and by Atromid (Duncan, Cullen, Ireland, Nolan, Clarke, and Oliver, 1968).

Four eyes (in two patients) had massive macular oedema with minimal lipoid deposition (Table III). When the oedema subsided a considerable degree of macular pigmentation was present. One of these four eyes showed a striking improvement in vision, but there was little change in the remainder.

Table III *Visual acuity in severe maculopathy*

Macular lesion	*Eye*	*Visual acuity*		*Greatest size of plaque in macular area (d.a.)*	*Final state of macula*
		Initial	*Final*		
Lipoid plaques	R	6/18	6/60	0·5	0·25 d.a. lipoid
	R	Counting fingers	3/60	2·5	Macular pigmentation—no lipoid
	L	6/24	5/60	2·0	Central fibrous scar—no lipoid
	L	6/60	6/9	0·5	No lipoid
	R	6/9	6/18	0·5	0·5 d.a. lipoid
	R	2/60	2/60	0·5	0·5 d.a. lipoid
	R	6/60	Hand movements	2·0	0·5 d.a. lipoid
	L	6/60	6/60	1·5	0·5 d.a. lipoid
	R	3/60	6/24	1·0	No lipoid
	L	6/9	6/36	0·5	0·25 d.a. lipoid
	R	6/36	6/36	1·5	No lipoid
	R	3/60	6/36	0·5	No lipoid
	L	Counting fingers	Counting fingers	4·0	No lipoid
	R	6/60	6/36	0·75	0·25 d.a. lipoid
Massive oedema without lipoid deposit	R	6/12	6/24	—	Macular pigmentation
	L	6/60	6/6	—	Macular pigmentation
	R	6/24	6/60	—	Macular pigmentation
	L	6/24	6/24	—	Macular pigmentation

d.a. = disc area

The change in visual acuity for all patients during the period of observation is given in Table II, which shows that the visual deterioration is very slow and supports the findings in the large series of cases reported by Caird and Garrett (1963). A comparison between the initial and final visual acuities demonstrates that a diminution in visual acuity in exudative retinopathy is usually permanent.

(III) Pathological veins and arterioles in exudative diabetic retinopathy

On one occasion at least, routine pictures of the retinal vascular tree as far as the equator were taken in every case. These can be compared with the vascular trees of 112 cases of proliferative retinopathy which were recently screened to determine the frequency of certain physical signs in that condition (Dobree, 1968b). In the proliferative series venous calibre abnormalities were common, whereas in the exudative group they were found only in the two eyes of Case 2. Pathological arterioles, which appeared as white lines on the photographs, in which the walls were replaced by connective tissue and the lumina were extremely narrow or absent (Davis, Myers, Engerman, de Venecia, and Magli, 1968) were found in 17·9 per cent. of cases of the proliferative series and in only one of the exudative series here reported.

In another study (Taylor and Dobree, 1969), it was found that the "true" new vessel formations in proliferative diabetic retinopathy are related to the larger retinal vessels, whereas the present study shows that the areas of capillary pathology are found mainly at the posterior pole and are not related to the larger vessels. This suggests that an essential difference, if not *the* essential difference, between simple and proliferative diabetic retinopathy lies in the fact that in simple diabetic retinopathy the angiopathy affects capillaries and in proliferative diabetic retinopathy the larger retinal vessels are involved.

(IV) Therapeutic considerations

From the facts that many of the ring forms of exudates surround foci of capillary damage and that serial tracings demonstrate the formation of plaques of exudates related to other foci, there can be little doubt that there is a direct relationship between the two.

Maumenee (1968) reviewed the controversial issue whether retinal lipoid deposits are due to neuronal degeneration consequent on capillary damage or on leakage from the damaged capillaries, and concluded that the fundamental pathological change is capillary leakage. The fluorescein studies of Gass (1968) already mentioned support this view. In either case the loss of vision in simple diabetic retinopathy is caused in the main by the deposition of lipoid and oedema in the macular area. Meyer-Schwickerath and Schott (1968) and Wessing and Meyer-Schwickerath (1968) reported favourably on the effects of light coagulation on the lesions of simple diabetic retinopathy, and Welsh (1968), describing the effect of photocoagulation of "aneurysmal and neovascular areas" in the centre of lipoid rings, reported improvement, sometimes dramatic, in those cases in which the ring involved the macula. Maumenee (1968), in cases of Coats's disease in which the lipoid deposits are similar but the leakage more copious, also reported marked improvement after light coagulation.

With a knowledge of the natural history of the disease, the following rationale is suggested:

(1) A case showing maculopathy should be reviewed by serial fundus photographs at as early a stage as possible in the disease.

(2) As the progress is very slow it is unnecessary to take immediate action on all areas of capillary damage as many of these do not have associated oedema or lipoid deposits and unless related to the macula such changes have little effect on vision.

(3) The most careful watch should be kept on capillary lesions just lateral to the macula and, should fluorescein studies or other evidence suggest macular involvement, these should be eradicated before extensive macular deposits form as the resultant visual loss is likely to be permanent.

(4) In the light-coagulation of such areas in the vicinity of the macula, *special caution should be exercised in limiting the extent of the coagulations* so as to avoid unnecessary damage to the arteriolar supply or venous drainage of the macular area. The writer has already seen two cases complicated by macular oedema caused by failure to observe this principle.

(5) As simple diabetic retinopathy runs a protracted course, the patient must be kept under constant review by serial photographs and fluorescein studies. Several coagulations spread over a long period of time may be indicated.

Summary

(1) The relationship between lipoid exudates and foci of pathological capillaries has been studied in fifty eyes over periods varying from 2 to 7 years.

(2) By superimposing tracings of foci of pathological capillaries and lipoid exudates, it has been shown that the capillary foci are very stable and that the lipoid exudates either surround them in ring forms or appear as clumps of deposit related to them. There is preferential "pooling" of lipoid in the macular area.

(3) Almost one-third of the foci of pathological capillaries was found in a small area just lateral to the macula.

(4) In general the foci of capillary damage of simple diabetic retinopathy lie in a different region of the retina from the new vessel formations of proliferative diabetic retinopathy.

(5) The permanence of the loss of vision after lipoid deposition or oedema of the macular area is stressed.

(6) With a knowledge of the spontaneous evolution of the lesions of simple diabetic retinopathy, a rationale of treatment by direct application of light energy to selected foci of pathological capillaries is suggested.

My thanks are due to Dr. Kenneth Black, Physician in Charge of the Diabetic Clinic at St. Bartholomew's Hospital, for his cooperation in this study; to Mr. P. G. Cull, of the Medical Illustration Department of St. Bartholomew's Hospital, for his advice in the making of the polythene transparencies and for the colour illustration; and to my Secretary, Miss T. Lister, for all her work in the preparation of this paper.

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Proliferative diabetic retinopathy

Site and size of initial lesions

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The pathogenesis of proliferative diabetic retinopathy is unknown. Although there are some established clinical and histological facts, the exact sequence of events is yet to be determined. Diabetic angiopathy is widespread in the body and appears to be a complication of and related to the duration of the diabetic state. The essential difference between this and proliferative diabetic retinopathy is the absence of microaneurysm formation and neovascularization outside the eye. It thus seems that local ocular factors, either genetic, metabolic, or anatomical, modify the generalized response. The role of the last factor has not yet been investigated, so that it is not known whether the anatomical pattern of the retinal arteries and veins has any relationship to the sites and size of areas of neovascularization.

It is the purpose of this paper to study the size and distribution of those areas in early proliferative diabetic retinopathy which are of sufficient size to be visible in fundus photographs and to subject them to statistical analysis to see if any definable pattern emerges.

Material

103 patients with proliferative diabetic retinopathy are under regular review with regard to their diabetic state and in particular the fundus changes. 170 eyes in these patients were studied. All fundi were photographed in multiple fields using the Zeiss fundus camera at about 3-monthly intervals. The data collected in this survey are taken from these photographic records made at the first or second visits.

Of the 170 eyes studied, 86 were suitable for inclusion in the present survey as the new vessels were in an early stage of formation. The remainder were excluded because the areas of proliferation were too diffuse and advanced at the initial visit and the origin of the new vessels was obscured or obliterated by connective tissue. The criteria for inclusion were:

(1) There were good photographic records of the fundus at the first or second visit.

(2) There was photographic continuity from the area of neovascularization to the optic disc, using one or more photographic fields.

(3) The site of origin of an area of neovascularization was discrete, so that the relationship of the feeding vessels to the main retinal vein and the optic disc could be accurately measured.

Method

A fixed projector was used to project the photographs a fixed distance onto a solid white wooden screen. All areas of neovascularization visible on the initial photographs were documented, thus giving a record of the lesions as they present to the ophthalmologist. A composite diagram was

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made for each eye to show two-dimensional relationships of the optic disc, retinal arteries and veins, and areas of neovascularization. The sites of the lesions were divided into three main groups:

(1) Arising from the optic disc.

(2) Isolated retinal lesions.

(3) Associated with a retinal vein.

The last group was further subdivided into the four main drainage areas, superior and inferior temporal and superior and inferior nasal.

The position of the lesion in the fundus was determined by the following measurements (Fig. 1):

(1) The distance along a vein from the disc margin to the origin of the feeding vessels (B).

(2) The distance along a vein from the disc margin to the arterio-venous crossing nearest to the lesion on the same vein (C).

(3) The radial distance of the lesion from the centre of the optic disc to the centre of the lesion (D).

(4) The angle subtended by a lesion from the centre of the optic disc.

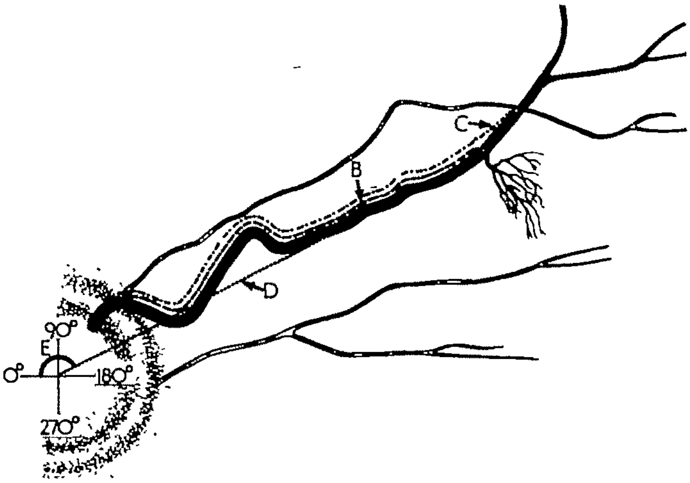

FIG. 1 *Drawing of sector of right fundus, showing measurements made to determine the site of new vessel formation*

(B) Distance along a vein from the disc margin to the site of a lesion

(C) Distance along a vein from the disc margin to the arterio-venous crossing nearest the lesion

(D) Radial distance from the centre of the optic disc to the centre of the lesion

(E) Angle

In the right eye, the angle was measured 0°–360° reading clockwise, 0° being at 9 o'clock on the fundus.

In the left eye a mirror image of the angle reading was made, thus 0° lay at 3 o'clock and was measured to 360° in an anti-clockwise direction.

By this means, for example, all lesions in the upper temporal field, whether in the right or left eye, lay between 0° and 90°, thus standardizing the results (see E in Fig. 1).

The linear measurements were made with an opisometer on the projected photograph on the wooden screen. The arbitrary figures so obtained were converted to disc diameters with reference to the opisometer measurement of the optic disc for the same eye.

A quantitative assessment was made of the size of the lesions. As the lesions are irregular in outline, the diameter varies in all directions, and therefore grouped estimates of these diameters were used.

Lesions were placed in four categories according to the diameter:

(1) Less than half a disc diameter.

(2) From half to one disc diameter.

(3) One to two disc diameters.

(4) Greater than two disc diameters.

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Results

A total of 248 new vessel formations were seen in the 86 eyes studied. Although the eye is a sphere, and the measurements have been made on a flat surface, the distortion is small and similar for all measurements, so that the comparison of the data is valid. The results are shown in Table I*.

These data have been subjected to a statistical analysis in respect of (*a*) distribution of lesions, (*b*) size of lesions, (*c*) distance of lesions from optic disc, and (*d*) relationship of lesions to arterio-venous crossings.

(*a*) *Distribution of lesions*

(1) GENERAL

There were 248 lesions in the 86 eyes; 63 (73·25 per cent.) showed lesions on the optic disc, and in 14 eyes the neovascularization was confined to this site.

The number of lesions associated with each of the four main venous drainage areas is shown in Table II. The number of isolated retinal lesions was very small, only nine out of 248. This group contained too few examples for any significant conclusions to be drawn, and it is therefore excluded from subsequent calculations.

Table II *Distribution of* 248 *areas of neovascularization in* 86 *eyes*

Site	*No. of lesions*
Optic disc	63
Upper temporal vein	63
Lower temporal vein	47
Lower nasal vein	29
Upper nasal vein	37
Isolated retinal	9

Table III *Distribution of lesions by size*

Size (disc diameters)	*On disc*	*On retinal veins*
$< \frac{1}{2}$	14	36
$\frac{1}{2}$–1	8	76
1–2	14	52
> 2	27	12

(2) AMONGST RETINAL VEINS

176 lesions were distributed amongst the four main branches of the retinal veins (Table II). This distribution is uneven, most lesions occurring in association with the superior temporal veins and fewest with the inferior nasal veins. This difference is significant ($\chi^2 = 14{\cdot}64$; 3 d.f.; $0{\cdot}01 > P > 0{\cdot}005$).

These findings can be represented pictorially, using the radial measurements and the angles of the lesions (Fig. 2, overleaf); this demonstrates clearly the lesions lying along the paths of the main vascular branches, with the greatest concentration in the superior temporal field.

The lesions related to the nasal vessels lie nearer the optic disc. Of particular interest is the fact that there are no proliferative lesions in the macular and paramacular areas.

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*Because Table I is very large and detailed it has been decided not to publish it with this paper. The data is available to anyone interested in this subject on application to the authors.

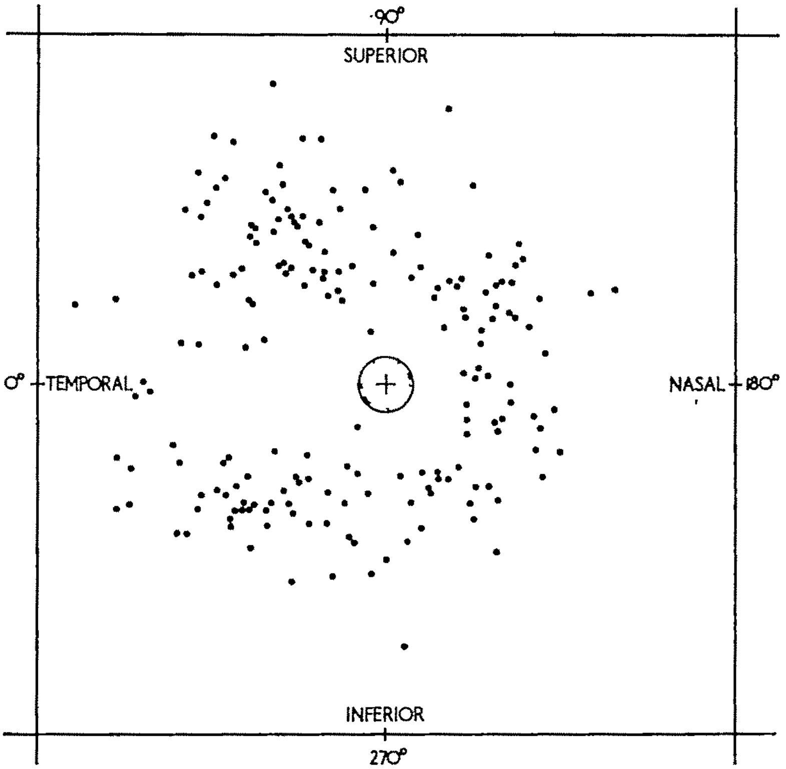

FIG. 2 *Schematic representation of the right fundus, showing points of origin of 185 areas of neovascularization surrounding the optic disc. The lesions in the left eye have been transposed laterally in order to include them in the same Figure*

(*b*) *Size of lesions*

The distribution of lesion size is shown in Table III. There were more of the larger lesions on the disc than in association with the retinal veins; thus 42·8 per cent. of disc lesions were greater than 2 disc diameters in size when first seen, whereas only 6·8 per cent. of the remaining lesions exceeded 2 disc diameters. These figures are highly significant ($\chi^2 = 49\cdot94$; 3 d.f.; $P \nless 0\cdot001$).

The distribution of lesion sizes amongst the four main retinal veins is shown in Table IV. The findings are not significant ($\chi^2 = 10\cdot35$; 9 d.f.; $0\cdot4 > P > 0\cdot3$). Thus there is no tendency for a lesion of a particular size to occur on a particular vein, but it is not possible to say whether this size scatter is truly random.

Table IV *Distribution of lesion sizes by site on retinal veins*

Size (disc diameters)	*Temporal*		*Nasal*	
	Superior	*Inferior*	*Inferior*	*Superior*
½	8	13	8	7
½–1	29	19	12	16
1–2	18	13	9	12
2	8	2	0	2

(*c*) *Distance of lesions on the veins from the optic disc* (Table V)

There was no significant difference in mean distance from the optic disc margin to the origin of the lesion between the superior and inferior temporal veins or between the superior and inferior nasal veins. It seemed reasonable, therefore, to combine the data into temporal and nasal groups as in Table VI. The difference between the mean distances in the temporal and nasal fields is now highly significant (Student's t test is 5·56, 174 d.f.; $P \nless 0{\cdot}001$). Thus lesions associated with temporal venous branches tend to occur further from the disc margin than those associated with nasal venous branches.

Table V *Site of lesions on veins, by distance from optic disc*

Site		*No. of lesions*	*Mean distance along vein from disc (disc diameters)*	*Variance*	*Standard deviation*
Temporal	Superior	63	3·44	1·55	1·245
	Inferior	47	3·24	1·45	1·204
Nasal	Inferior	29	2·21	0·55	0·741
	Superior	37	2·46	0·95	0·972

Table VI *Site of lesions on veins related to distance from optic disc, temporal and nasal groups combined*

Site	*No. of lesions*	*Mean distance along vein from disc (disc diameters)*	*Variance*	*Standard deviation*
Temporal	110	3·36	1·50	1·22
Nasal	66	2·35	0 76	0·87

(*d*) *Distribution of lesions related to arterio-venous crossings*

The measurements used for this analysis are the distance from the margin of the optic disc to the lesion, and from the margin of the optic disc to the arterio-venous crossing nearest to the lesion. 176 lesions were clearly associated with the retinal veins (see *a*1 and *a*2, above). Of these, 129 have a crossing nearby on the same vein. On twelve occasions, two lesions were associated in pairs with the same arterio-venous crossing, making a further 24 lesions. There were only two instances in which three areas of neovascularization were grouped around a single arterio-venous crossing, making six lesions in all. The lesions lay on the disc side of the crossing in sixty cases, and peripheral to it in 99 cases. One other lesion has been excluded, as the only arterio-venous crossing was associated with a different branch of the same vein.

The remaining sixteen areas of neovascularization have no crossing on the vein at any point. All of these except one lie in the nasal field, six superior and nine inferior.

The 159 lesions associated with an arterio-venous crossing have been used in the analysis. The distances from the optic disc to the lesion and from the optic disc to the arterio-venous crossing have been plotted as the co-ordinates of a graph (Fig. 3, overleaf). This shows

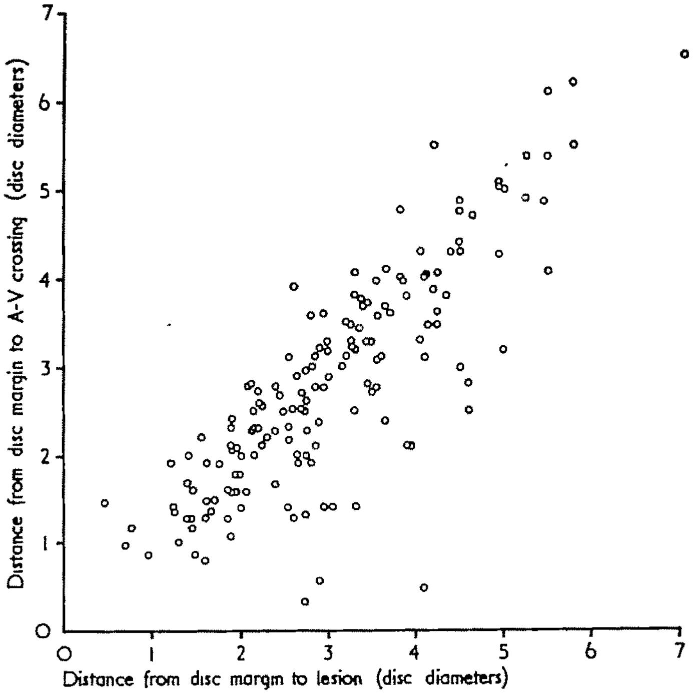

FIG. 3 *Graph showing a high degree of correlation between site of lesion and nearest arterio-venous crossing*

that the points fall close to a straight line, thus showing a high degree of correlation between the two measurements—*i.e.* the lesions are related to the crossings and are not therefore randomly distributed.

Discussion

Venous and capillary changes in proliferative diabetic retinopathy were originally thought to represent localized limited venous thromboses, and Bonnet and Bonamour (1938) described the retinal changes in several cases of diabetes mellitus to support this theory. They particularly noted neovascularization at an arterio-venous crossing in two cases. Ashton (1963) showed that the early changes in proliferative diabetic retinopathy of micro-aneurysm formation and neovascularization are seen histologically in many other systemic and ocular disorders. They should therefore be regarded as a response to similar stimuli (Ashton, 1967). He has further suggested that this stimulus is a vaso-formative factor released from localized areas of hypoxic retina. Wise (1956) had previously supported the existence of an unknown factor (Michaelson's X factor, 1954), which stimulated new vessel formation, and he believed that it was produced in all cases of retinal neovascularization, and that moreover the underlying pathological state responsible for its production was venous obstruction.

In this anatomical survey, we have found that areas of neovascularization arise from the disc and from the main temporal and nasal veins. With regard to the venous lesions the following points were noted:

(1) Lesions occur more frequently on the temporal than on the nasal veins;

(2) Lesions are most commonly seen on the superior temporal veins;

(3) Temporal lesions lie farther from the disc margin than nasal lesions;

(4) All the temporal lesions except one, and 80 per cent. of the nasal lesions, are associated with an arterio-venous crossing;

(5) A high degree of correlation exists between the lesion and the site of an arterio-venous crossing.

Koyanagi (1928a, b) found a greater number of arterio-venous crossings associated with the superior temporal vein than in any other venous drainage area. It is therefore reasonable to postulate that the larger number of arterio-venous crossings in the superior temporal field predisposes to the larger number of lesions found in this venous drainage field.

Dobree (1964) reported that thirteen out of 25 eyes (52 per cent.) showed disc neovascularization at the initial visit, but in the present series the incidence is 73·25 per cent. Moreover, at the initial visit, disc lesions are larger than those arising from retinal veins.

As Fig. 2 demonstrates, proliferative lesions were absent over the posterior pole. This is in contrast to the angiopathy found in a recent study of exudative retinopathy by Dobree (1970). In this it was found that the foci of pathological capillaries in exudative diabetic retinopathy lie preferentially at the posterior pole, especially lateral to the macula. This also confirms our clinical finding that exudative and proliferative lesions do not overlap anatomically.

An analysis of our results indicates that the development of lesions in proliferative diabetic retinopathy does not occur at random. The distribution of the site and size of disc and retinal lesions show distinctive features, and a positive correlation exists between the lesions associated with the retinal veins and the arterio-venous crossings. Although in this series no subdivision of lesion site on the optic disc has been made, it may be relevant that there are arterio-venous crossings on all discs. The answer to the question whether these results can be grouped under one aetiological factor awaits further study. The most likely supposition is that this factor is of a mechanical nature, such as a localized disturbance in haemodynamics at the arterio-venous crossing, thus affecting the blood flow and oxygenation in a localized area of the retina. Alternatively, it may be a purely mechanical obstruction to blood flow, and the areas of neovascularization are primarily anastomotic in nature. In either case, it is the mechanical factor leading to localized metabolic disturbance within the retina which determines the site of the initial lesion.

Summary

The initial photographs of 86 eyes with proliferative diabetic retinopathy have been studied. A statistical survey has been carried out with respect to the site and size of 248 areas of neovascularization. The following observations were made:

(1) 73·25 per cent. of eyes have areas of new vessel formation on the optic disc and these areas are larger than those associated with retinal veins.

(2) Lesions associated with retinal veins show the following characteristics:

(*a*) They occur most frequently on the superior temporal veins,

(*b*) Temporal lesions lie farther from the optic disc than nasal lesions,

(*c*) A high degree of correlation exists between the site of a lesion and the nearest arterio-venous crossing.

We wish to thank Dr. Alan Jennings for assistance with the statistical analysis and Miss Christine Otway for secretarial help.

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Provocative outflow test

Combining water drinking and homatropine

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We have combined instillation of guttae homatropine 2 per cent. with water drinking as a new and more powerful provocative test in a series of 24 patients suspected of open-angle glaucoma in order to compare their effect on ocular tension and facility of outflow with the effect of guttae homatropine alone and water drinking alone. The amount of water given to each patient was varied according to body weight, 20 ml./kg. being given, with the object of decreasing the variance of the observations. Spaeth (1967) used 14 ml./kg. in his water drinking tonometry test.

Becker and Christensen (1956) demonstrated a greater fall in C after one litre of water in 188 cases of open-angle glaucoma than in 175 normal eyes; a Po/C> 100 was found in 97 per cent. of glaucomatous eyes and only 1 per cent. of normal eyes. Galin, Aizawa, and McLean (1961), however, could not find a significant fall in the outflow facility of 41 cases of glaucoma after 1 litre of water.

Christensen and Pearce (1963) reported a rise in tension after guttae homatropine 5 per cent. in open-angle glaucoma. This occurred only occasionally in normal eyes in which there was usually a fall. It was accompanied by a fall in the outflow facility in 28 per cent. of glaucomatous and 15 per cent. of normal eyes. Bárány and Christensen (1967) demonstrated an increase in the outflow resistance in normal and glaucomatous human eyes after cycloplegia with guttae homatropine 5 per cent.; the effect was greater in patients with open-angle glaucoma than in normal subjects and there was a small overlap between these two groups.

Kirsch (1965) and then Kristensen (1967) combined a dark-room test with water drinking and mydriasis as a provocative test in suspected closed-angle glaucoma.

Methods

The test subjects were 24 patients suspected of open-angle glaucoma who had borderline or raised ocular tensions and/or discs which were considered suspicious of glaucoma. All had open angles and any patient with angles judged to be in danger of becoming closed by mydriasis was excluded.

Each attended as an out-patient on three separate mornings, the same eye being tested on each occasion. When water was to be taken, the patient was told to have nothing to eat or drink from the previous evening. In all, thirteen right and eleven left eyes were chosen at random for investigation by the toss of a coin except for one in which corneal opacities were present in one eye.

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The procedure was as follows:

(1) Applanation tension.
(2) Schiotz tension.
(3) 4-minute tonography.
(4) One of the following at each visit:
  (*a*) Water by mouth (20 ml./kg. body weight)
  or
  (*b*) Guttae homatropine 2 per cent. to the eye for testing
  or
  (*c*) Both (*a*) and (*b*).

then, after 45 minutes,

(5) Applanation tension.
(6) Schiotz tension.
(7) 4-minute tonography.

These tests were carried out by a technician using a Schwarzer electronic tonometer. The order of these three tests *a*, *b*, and *c* under (4) above was randomized. There are six possible different sequences, so that four subjects were allotted to each sequence (see Table I).

Table I *Order in which tests were carried out*

Sequence		*I*	*II*	*III*	*IV*	*V*	*VI*	
Order	1st visit	*a*	*b*	*c*	*c*	*b*	*a*	see key below
of	2nd visit	*b*	*c*	*a*	*b*	*a*	*c*	
tests	3rd visit	*c*	*a*	*b*	*a*	*c*	*b*	
No. of subjects allotted to each		4	4	4	4	4	4	Total no. of subjects 24

a = Water drinking tonography test
b = Homatropine tonography test
c = Water drinking homatropine tonography test

Results and discussion

Table II compares pre- and post-provocation values of C, Po, etc. for each test on individual eyes, *i.e.* "within test" differences, and Table III compares the effects of one test with another. Statistical evaluation of the results was by the Wilcoxon Matched Pairs Signed Ranks Test (Siegel, 1956). This is non-parametric and suitable to the data because a normal distribution does not have to be assumed. A two-tailed version of this test was used. The Wilcoxon T score is given for each of the tests. The lower the T score, the less likely this is to arise by chance. The borderline of significance has been taken as P = 0·05, and for clarity the Wilcoxon T score for this probability is added in brackets for each result in the tables.

(*1*) *Fall in outflow facility "C"* (uncorrected for ocular rigidity K)

The fall in C for the homatropine tonography test and also the water drinking homatropine tonography test was significant (P <0·01) in each case. Surprisingly there was no significant fall for the water drinking tonography test. The magnitude of the fall was significantly greater for the water drinking homatropine tonography test than for the water drinking tonography test (T = 67½; 0·02 < P < 0·05; T corresponding to P = 0·05 is 73). In neither of the other two between-test comparisons was there a significant difference (Table III).

Table II *"Within test" differences. Comparison of immediately pre-test values of C, Po, R, Po/C, and Flow, with these values after 45 minutes. 24 subjects*

Test	*Water drinking tonography*			*Homatropine tonography*			*Water drinking homatropine tonography*		
	Wilcoxon T score		P	*Wilcoxon T score*		P	*Wilcoxon T score*		P
Fall in C	103½	(81)	> 0·05 (NS)	37	(81)	< 0·01 (S)	30½	(81)	< 0·01 (S)
Rise in Po	7	(66)	< 0·01 (S)	41	(40)	> 0·05 (NS)	0	(81)	< 0·01 (S)
Rise in R	83½	(81)	> 0·05 (NS)	41½	(81)	< 0·01 (S)	34½	(81)	< 0·01 (S)
Rise in Po/C	57	(73)	< 0·01 (S)	42½	(81)	< 0·01 (S)	8	(81)	< 0·01 (S)
Rise/Fall in Flow	111 Rise	(81)	> 0·05 (NS)	49½ Fall	(81)	< 0·01 (S)	146 Fall	(81)	> 0·05 (NS)

S = significant; P < 0·05. NS = not significant; P > 0·05. Figure in brackets represents T score for P = 0·05, *i.e.* borderline of significance for that particular test.

When T is less than 81, a tie or ties have occurred, so that the number of ranks for that particular test is reduced.

Table III *"Between test" differences in the same 24 subjects as in Table II*

Comparison of tests	*Water drinking tonography versus Homatropine tonography*			*Homatropine tonography versus Water drinking homatropine tonography*			*Water drinking tonography versus Water drinking homatropine tonography*		
	Wilcoxon T score		P	*Wilcoxon T score*		P	*Wilcoxon T score*		P
Fall in C	90½	(73)	$>0{\cdot}0\overset{+}{5}$ (NS)	140½	(73)	$>0{\cdot}0\overset{+}{5}$ (NS)	67½	(73)	$0{\cdot}02<P<0{\cdot}0\overset{+}{5}$ (S)
Rise in Po	7½	(40)	$<0{\cdot}0\overset{*}{1}$ (S)	0	(81)	$<0{\cdot}0\overset{+}{1}$ (S)	28	(52)	$<0{\cdot}0\overset{+}{1}$ (S)
Rise in R	103	(81)	$>0{\cdot}0\overset{+}{5}$ (NS)	133	(81)	$>0{\cdot}0\overset{+}{5}$ (NS)	88	(81)	$>0{\cdot}0\overset{+}{5}$ (NS)
Rise in Po/C	192	(81)	$>0{\cdot}0\overset{+}{5}$ (NS)	88	(81)	$>0{\cdot}0\overset{+}{5}$ (NS)	74	(81)	$0{\cdot}02<P<0{\cdot}0\overset{+}{5}$ (S)
Fall in flow	48	(81)	$<0{\cdot}0\overset{+}{1}$ (S)	102	(81)	$>0{\cdot}0\overset{*}{5}$ (NS)	115	(81)	$>0{\cdot}0\overset{+}{5}$ (NS)

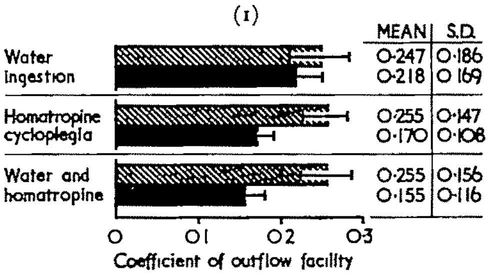
+ = result favours test mentioned second at head of column.
* = result favours test mentioned first at head of column.
S = significant; P < 0·05. NS = not significant; P > 0·05. 0·02 < P < 0·05 means P between 0·02 and 0·05.

Figure in brackets represents T score for P = 0·05, borderline of significance for that particular test comparison.

When T is less than 81, a tie has occurred, so that the number of ranks for that particular test comparison is reduced.

Fig. 1 (overleaf) shows the changes in C for the three tests in the form of bar charts. Means and standard deviations are indicated. The results were not normally distributed, as Prijot (1961) has already found.

In Fig. 2 (overleaf), the changes in C are shown in chronological order of performance, *i.e.* irrespective of which test was done on a particular visit. The initial C values became progressively smaller from Visit 1 to Visit 3 but the maximum difference, *i.e.* between Visit 1 and Visit 3 was not significant (T = 97½. A T of 81 is required for P = 0·05). This probably explains the fact that for Visit 3 the provocation-induced fall in C is least, although it is not significantly less than for Visit 1 (T = 120; T (0·05) = 81). This interesting trend is presumably due in some way to habituation of the patient (rather than to the weather, experience of the tonographer, etc.) and it underlines the importance of our rigid randomization (!) of the order of our series of tests—note the remarkably standard average of initial C in Fig. 1.



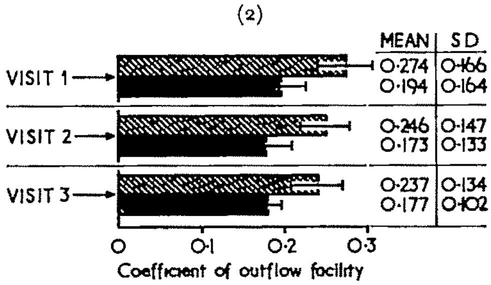


FIG. 1 *Bar Chart showing outflow facility in 24 subjects, before and after provocation for:*

(*a*) Water drinking tonography test;
(*b*) Homatropine tonography test;
(*c*) Water drinking combined with homatropine tonography test.

The standard error of the mean is indicated on each bar.

To the Wilcoxon Matched Pairs Signed Ranks Test there was a significant fall in the outflow facility for (*b*) and (*c*) at $P < 0{\cdot}01$, but no significant fall for (*a*) ($P > 0{\cdot}05$). The fall was significantly greater for (*c*) than for (*a*) ($0{\cdot}02 < P < 0{\cdot}05$).

FIG. 2 *Bar Chart showing outflow facility in 24 subjects, before and after provocation for:*

(*a*) Visit 1
(*b*) Visit 2
(*c*) Visit 3, *i.e.* irrespective of which test was done on a particular visit.

The standard error of the mean is indicated on each bar.

Note that initial tonography appears to show a steady decrease from Visit 1 to Visit 3, which is the main factor in reducing the test response; however, the change in outflow facility at Visit 3 was not significantly less than at Visit 1 (Wilcoxon Matched Pairs Signed Ranks Test).

In the determination of outflow facility, the 5·5 g. weight was used throughout the tests, except for the post-provocation values in four water drinking homatropine tonography tests, when the 7·5 g. weight was used. However the total fall in C in the water drinking tonography test for these four individuals when the 5·5 g. weight was used consistently was greater than in the water drinking homatropine tonography test; accordingly, the use of the 7·5 g. weight is unlikely to have biased the results in favour of the latter test.

(2) *Rise in Po applanation tension*

Obviously the changes in ocular tension during the water drinking tonography test are not comparable with those in a conventional water drinking *tonometry* test because of the effect of the initial tonography, but examination of these data was of interest. For both the water drinking tonography test and the water drinking homatropine tonography test, the rise in Po was significant (see "Within test" differences, Table II), that for the latter being significantly greater ($P < 0{\cdot}01$) (see "Between test" differences, Table III).

In the homatropine tonography test, the rise in Po was not quite significant, although the fall in C, rise in R (outflow resistance), and rise in Po/C had all been significant. It is worthy of note that the water drinking homatropine tonography test produced a greater rise in Po than the homatropine tonography test in all 24 cases. Therefore water loading in addition to cycloplegia was required to increase the tension within the test. This was well illustrated by estimation of aqueous flow with the formula (Gloster, 1966): Flow = C (Po-Pv), where Pv is the episcleral venous pressure. This was assumed to be 11 mm. Hg throughout the tests; there is general agreement in the literature that it lies in the region of 10 to 12 mm. (Gloster, 1966). The assumptions here are probably large, but the concept is useful in this context. On this basis (see Tables II and III), a significant fall in flow occurred between the first and second tonographies in the homatropine tonography test. In the water drinking tonography test there was a net rise, which was not significant, and in the water drinking homatropine tonography test the change in flow was negligible, a slight fall being found. The difference in change of flow between the water drinking tonography and homatropine tonography tests was significant, the latter giving the greater fall. This absence of rise in tension and apparent fall in aqueous flow in homatropine tonography raises interesting possible explanations like the opening up of unconventional aqueous outflow channels (Bill, 1966) and the reduction of aqueous formation by homatropine cycloplegia, but they may quite simply be due to the hypotensive effect of the initial tonography. To clarify this point would require a comparison of the homatropine tonography test with a further test situation involving two tonographies with an interval of 45 min. between them, but no medication, etc.; in the latter case the Po of the second tonography might well not have had time to return to the level at the start of the first tonography.

(3) *Rise in outflow resistance R*

R is the reciprocal of C (Gloster, 1966). The rise in R for the water drinking tonography test was not significant, but this time the water drinking homatropine tonography test was not significantly more effective than the water drinking tonography test in increasing R, whereas it had been more effective in reducing C. The different result when the reciprocal is used was probably due to some tests in which the rise in resistance was large compared with the corresponding fall in C or *vice versa.*

Bárány and Christensen (1967), in their examination of similar data for a homatropine tonography test, quoting Prijot (1961), plotted logarithms of the outflow resistance so as to obtain a nearer approximation to a normal distribution. Fig. 3 shows a graph of

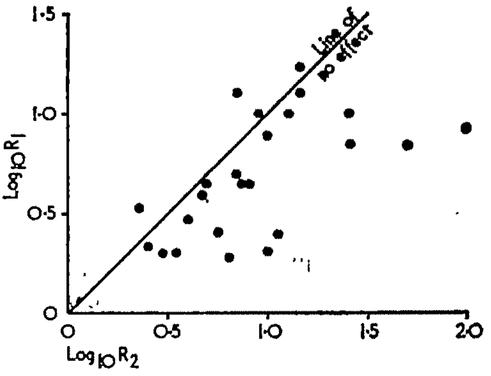


FIG. 3 *Scattergram of log_{10} outflow resistance in 24 subjects.*

R_1 before and R_2 after provocation with water drinking combined with instillation of guttae homatropine

$\log_{10}$ R from our data before and after water *and* homatropine. The distribution of points is very similar to that recorded by Bárány and Christensen (1967) for homatropine tonography. A normal distribution for these results being assumed, a Student's t test was done for $\log_{10}$ R in the water drinking homatropine tonography and the water drinking tonography test. This indicated a significantly greater rise in R for the former than for the latter ($t = 2{\cdot}35$; $0{\cdot}02 < P < 0{\cdot}05$). With data from eleven additional subjects who had had the homatropine tonography test and water drinking homatropine tonography test only, *i.e.* 35 subjects in all, a Student's t test for rise in $\log_{10}$ R was done. This gave a significantly greater rise in outflow resistance for the water drinking homatropine tonography test than for the homatropine tonography test. ($t = 2{\cdot}158$; $P = 0{\cdot}02 < P < 0{\cdot}05$). Unfortunately, these results are open to criticism because the tests were not randomized, 21 patients having had the homatropine tonography test first and fourteen the water drinking homatropine tonography test first. However, this does constitute some additional evidence that water combined with homatropine provided the most effective provocation of all three tried in this series.

(4) *Rise in Po/C*

In all three tests a significant rise was found, and that for the water drinking homatropine tonography test was significantly greater than in the water drinking tonography test ($0{\cdot}02 < P < 0{\cdot}05$).

(5) *Changes in ocular rigidity K*

During water drinking tests, Becker and Gay (1959), in patients suspected of open-angle glaucoma, reported a significant fall in K, and Drance (1963) a more frequent fall in K in glaucomatous than in normal eyes. Drance used his own formula (Drance, 1960) for estimating K.

In these tests, K was estimated by Friedenwald's Nomogram (1955 calibration) and paired applanation and Schiötz readings.

Our tests differ from a conventional water drinking tonometry test in that a 4-minute tonography has been carried out after the initial tension readings and before the ingestion of water and/or the instillation of guttae homatropine. The direction of changes in K did not show a significant trend towards either an increase or a decrease (Sign test; see Siegel ,1956).

Further discussion

In the practical clinical care of patients with the overt manifestations of glaucoma, we need to place little or no reliance on provocative tests, and to use tonography to a very limited extent. However, our responsibility for assessing at least the first-degree relatives of our patients with glaucoma as well as borderline cases has re-awakened our interest in provocative tests; hence the present study of a new combination of two known methods, *viz.* water drinking and homatropine.

In so far as the greatest change in "ocular fluid dynamics" was produced by the water drinking homatropine tonography test, it seems likely that this would be the best of the three tests examined here in differentiating a normal from a glaucoma population. A separate study of a series of normal subjects and patients with glaucoma would, of course, be required to define criteria of normality and judge the discriminating value of the tests.

(To assess the test's value in predicting ultimate glaucoma, a cohort study of a large population would be required.)

The mechanism by which water drinking reduces the C value is presumably related to decreased osmolality of the blood, which causes either increased production of aqueous or decreased outflow, presumably because of the swelling of the trabecular meshwork, or both, although the evidence for this is circumstantial. It is interesting that Spaeth (1967) showed that, in 20 per cent. of his 234 water drinking tests, the rise in ocular tension actually preceded the decrease in serum osmolality. A more indirect mechanism may therefore be involved.

Graphs were drawn to plot test responses against body weight (as a check on whether our linearly weight-related dose of water was effective) and against age (to check whether poorer absorption might occur as age increased), but inspection suggested no correlation.

In practice, a test involving two tonographies with only 45 minutes between them is rather unpleasant for the patient and time-consuming for the examiners, and also has the intrinsic disadvantage that the state of the eye after the first tonography must be somewhat altered even when the second tonography is done 45 minutes later. For all these reasons, a water drinking homatropine *applanation* test may be more practical, even if not clearly better than the water drinking homatropine *tonography* test assessed above, and these two tests are at present being compared in another series. The possibility of using an injection of hypotonic saline and/or pitressin is being considered. We have also found some evidence that the rise in ocular tension produced by water is less in a large eyeball than in a small one, as would be expected, and more data are being accumulated for this study.

Summary

In each of 24 "open-angle glaucoma suspects", an initial tonography on one eye was immediately followed by provocation,

viz.: (*a*) water by mouth (20 ml./kg. body weight),
(*b*) guttae homatropine 2 per cent.,
or
(*c*) both (*a*) and (*b*),

in strictly randomized order, and a second tonography was done on the same eye 45 minutes later.

The most effective test in producing a fall in the C value was the water drinking homatropine tonography test (see Fig. 1 and Table III) and the difference was statistically significant for the comparison of (*c*) with (*a*) but not with (*b*). The inclusion of eleven additional cases, not strictly randomized however, showed that (*c*) was significantly more effective than (*b*) in increasing resistance to outflow. The effect of the tests on Po (see Table III) was significant in all the comparisons,

viz.: (*c*) greater rise than (*b*)
(*c*) greater rise than (*a*)
(*a*) greater rise than (*b*).

Because of the disadvantages in a test requiring two tonographies with an interval of only 45 minutes, a separate study is being done to assess whether a water drinking homatropine *applanation* test may be as good as or better than a water drinking homatropine *tonography* test.

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Infantile glaucoma

Steroid testing in parents of affected children

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An important hereditary influence in open-angle glaucoma is already known to exist. At present the most powerful means of making manifest the presence of such a trait is probably the application of topical cortisone, which produces a marked rise in ocular tension in susceptible individuals, *i.e.* principally in cases of open-angle glaucoma (Armaly, 1963) and their relatives (Becker and Hahn, 1964). The magnitude and frequency of this rise in open-angle glaucoma has been shown to be greater than in a control sample (Armaly, 1965). Armaly (1966) has also shown that the ocular hypertensive response is itself genetically determined, possibly as a recessive trait.

Since the parents of children with infantile glaucoma are presumably heterozygous for the gene responsible, the condition being recessive, it seemed worthwhile to test their response to topical dexamethasone in order to establish whether or not the carrier state of a gene producing infantile glaucoma shares with open-angle glaucoma the property of a hypertensive response.

Methods

Index patients were thirteen males and five females with infantile glaucoma. Parents of these children were invited to attend for examination. In all, 35 parents (*i.e.* seventeen marital pairs and one mother) were seen and examined at an initial visit, and 28 re-attended after a course of guttae dexamethasone 0·1 per cent. three times a day for 3 weeks.

At the first visit the following procedure was carried out:

(1) A general, ocular, and family history was taken.

(2) The optic discs and fundi were examined.

(3) A slit-lamp examination was performed.

(4) Applanation tensions, *i.e.* three readings, were taken from each eye, right eye first, the middle reading in order of magnitude being noted.

(5) The angles were examined with a gonioscope.

Subjects were then given guttae dexamethasone* 0·1 per cent. to be instilled three times daily into one eye for 3 weeks, and were asked to re-attend after that time for repeat applanation tensions. Only 28 out of the possible total of 36 completed the course of guttae dexamethasone. The reasons for this discrepancy are set out overleaf:

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* This was made up from dexamethasone sodium phosphate, a 0·1 per cent. solution being obtained by the addition of a 0·5 per cent. solution of chlorbutol (Trade name: Decadron, Merck, Sharpe and Dohme Limited).

Number of index patients		18
Total possible number of parents who could be examined		36
Actual number of parents who came for *initial* assessment (one father did not attend)		35
Number found unsuitable for dexamethasone	1	35
Number who failed to attend for *second* visit	6	
Total who *completed* course of dexamethasone	28	
Number who completed course of dexamethasone (28)	males	females
12 complete marital pairs	12	12
4 incomplete marital pairs (*i.e.* only one parent completed tests)	2	2
Total	14	14

24 controls from the Outpatient Department, parents of patients who had squints, were matched for sex and age (within the range +5 to −6 years; the average age difference was minus 0·5 years) with 24 of the parents of affected children, and completed the same course of dexamethasone. It was difficult to achieve 28 controls because defaulting was common after the initial agreement to use dexamethasone.

Results

(1) HISTORY

(*a*) *Consanguinity*

Perhaps rather surprisingly, none was noted in any of the parents interviewed.

(*b*) *Family history*

In the eighteen families investigated in this way, there were 21 siblings of affected children, and none of these had glaucoma. In only one family was there a second affected member and this was an example of dominance or pseudo-dominance (Waardenburg, Franceschetti, and Klein, 1961), the male index patient having had a daughter with unilateral infantile glaucoma.

(2) RESPONSE OF OCULAR TENSION TO GUTTAE DEXAMETHASONE

The mean tension in the test eyes of parents of patients with infantile glaucoma was 16·32 mm. Hg applanation before and 18·36 mm. Hg after dexamethasone: the corresponding figures for the controls were 15·08 and 18·63 (Table I).

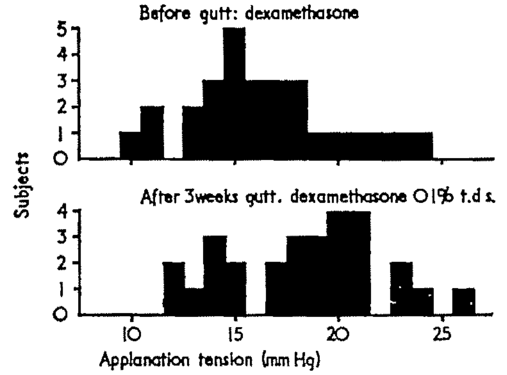
Table I *Ocular tension (mm. Hg applanation) before and after a 3-week course of dexamethasone*

Visit		1				2			
Eye		*Test*		*Contralateral*		*Test*		*Contralateral*	
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Series	28 parents	16·32	3·51	16·29	3·33	18·36	3·68	16·11	3·53
	24 controls	15·08	3·62	14·92	3·11	18·63	2·89	14·54	4·05

SD = Standard deviation

Of the 28 parents and 24 controls, the tension fell in five and three instances respectively and remained the same in three and one. Inadequate instillation of drops may, of course, be the explanation for the lack of rise in these cases. These differences in the direction of change in tension between parents and controls were statistically non-significant ($\chi^2 = 1{\cdot}54$; $n = 2$; $0{\cdot}3 < p < 0{\cdot}5$).

These observations are shown in the histograms in Figs 1 and 2 as a "shift to the right". The standard deviations before and after treatment were similar.



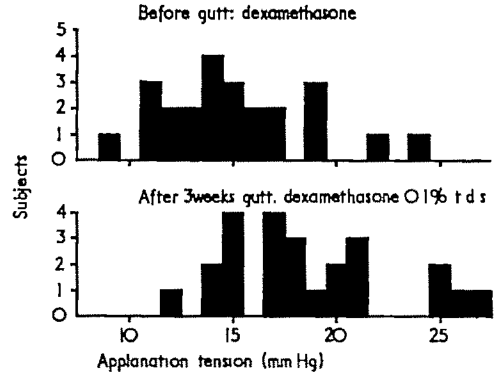


FIG. 1 *Applanation tensions of parents of affected children before and after guttae dexamethasone* 0·1 *per cent. three times daily for* 3 *weeks. Note a "shift to the right", indicating an ocular hypertensive response, which is quantitatively similar to that in Fig.* 2

FIG. 2 *Applanation tensions of controls before and after guttae dexamethasone* 0·1 *per cent. three times daily for* 3 *weeks. Note a "shift to the right", indicating an ocular hypertensive response, which is quantitatively similar to that in Fig.* 1

In a Wilcoxon Matched Pairs Signed Ranks Test (Siegel, 1956), the rise in tension was significant in the parents of affected children and also in the controls (P < 0·01) (See Table II).

Table II *Statistical analysis of changes in ocular tension (see Table I) of test and control (contralateral) eyes after a 3-week course of dexamethasone (Wilcoxon score)*

Eye	*Change in ocular tension*	*Series*					
		T	*T* (0·05)	P	*T*	*T* (0·05)	P
(1) Test	Rise	51½	89	< ·01*	32	73	< ·01*
(2) Test "allowing for change in tension of contralateral eye"	Rise	30	81	< ·01*	33	89	< ·01*
(3) Contralateral untreated	Fall	118	66	> ·05	83	52	> ·05

* difference statistically significant (P < 0·01).
T (0·05) refers to the Wilcoxon score for a probability of P = 0·05 for each test.

Table I shows that, in the contralateral untreated eyes, the ocular tension tended to fall, though not significantly (Table II). This fall in tension of the untreated eye would presumably have been paralleled by a fall in the tension of the test eye if dexamethasone had not been given, and so the fall in the former between Visit 1 and Visit 2 was taken into account in estimating the rise in tension of the test eye after dexamethasone; *e.g.* if the tension in the contralateral eye had fallen from, say, 13 to 11 mm. Hg between Visits 1 and 2, and the tension in the test eye had risen from 14 to 18 mm. Hg, then the rise in the latter, taking account of the fall in the former, would have been taken as (4 + 2) = 6 mm. Hg. A Wilcoxon Test was done on the results expressed in this way between test eyes and untreated eyes in each individual, and again the results were significant for a rise in tension at P < 0·01 in both parents and controls (Table II).

However, the magnitude of the rise in pressure in (*a*) parents as compared with (*b*) controls did not differ significantly (to a Mann-Whitney U Test (Siegel, 1956) $Z = 1 \cdot 32$; $U = 264$; $P = 0 \cdot 0934$). To a Wilcoxon Test, the 24 parents having been carefully matched with 24 of the controls, the absence of a significant difference in the magnitude of the dexamethasone response was confirmed ($T = 88$; T for $P = 0 \cdot 05$ would have been 66; $P > 0 \cdot 05$). Similarly, there was no significant sex difference in the response to dexamethasone.

(3) ANGLE OF ANTERIOR CHAMBER

Although one might have suspected that the parents of children with infantile glaucoma would have abnormal tissue in the angles revealing their heterozygous or carrier state, with only one exception, none was present. Angle appearances, therefore, seem to have no value in the detection of the carrier state.

Discussion

No toxic effects of dexamethasone were noted.

The ratio of 18 affected children: 21 normal children in affected families should not be interpreted as favouring a dominant heredity, or as contradicting the generally accepted recessive pattern with a 40 to 60 per cent. penetrance (Waardenburg, Franceschetti, and Klein, 1961). Of the 21 siblings of patients, only two were younger than the index patients. This is probably related to the fact that parents of affected children were informed early in the treatment of their child that, although some cases may not be hereditary, there was statistical evidence that a risk existed to further children of the order of 1 in 8 (recessive gene with 50 per cent. penetrance). If the parents decide that such a risk is too great, only one abnormal child is likely in each family, and this, coupled with the small size of the modern family, must increase the expected 1 : 8 ratio of affected to unaffected children in affected sibships.

The sex ratio of affected children (13 males : 5 females) favours males and this has frequently been found in other series (Shaffer, 1967, mentions 70 per cent.); the sex ratio of their 21 unaffected siblings was 8 males : 13 females. This sex difference was statistically significant ($\chi^2 = 4 \cdot 55$; $n = 1$; $0 \cdot 02 < P < 0 \cdot 05$).

Summary

The response of ocular tension to guttae dexamethasone 0·1 per cent. instilled three times daily for 3 weeks was similar in (*a*) parents of children with infantile glaucoma and (*b*) controls who had been closely matched for age and sex.

Accordingly, as judged by the dexamethasone response, the genetic carrier state for infantile glaucoma is not related to open-angle glaucoma.

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Sjögren's syndrome in relation to pernicious anaemia and idiopathic Addison's disease

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Lymphocytic infiltration of the gastric mucosa in chronic gastritis is associated with the development of pernicious anaemia in a proportion of cases (Anderson, Buchanan, and Goudie, 1967). More than 40 per cent. of patients suffering from pernicious anaemia can be shown to have antibodies to gastric parietal cells (Irvine, Davies, Delamore, and Williams, 1962; Markson and Moore, 1962; Taylor, Roitt, Doniach, Couchman, and Shapland, 1962; Irvine, 1963a). It occurred to the investigators that the lymphocytic infiltration in chronic gastritis might be similar to that found in the lacrimal and salivary glands in Sjögren's syndrome and it is to be noted that a series of patients suffering from this disease was found to have a high incidence of autoantibodies to gastric parietal cells (Buchanan, Cox, Harden, Glen, Anderson, and Gray, 1966). Furthermore, patients suffering from pernicious anaemia have a high incidence of thyroglobulin antibodies (Irvine and others, 1962; Markson and Moore, 1962; Taylor and others, 1962; Doniach, Roitt, and Taylor, 1963) as do patients with Sjögren's syndrome (Anderson, Goudie, Gray, and Buchanan, 1961; Bloch, Buchanan, Wohl, and Bunim, 1965).

Sjögren's syndrome consists of the triad of keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis (Sjögren, 1933) or other connective-tissue diseases such as systemic lupus erythematosus (Ramage and Kinnear, 1956; Bain, 1960), polyarteritis nodosa (Ramage and Kinnear, 1956), progressive systemic sclerosis (Ramage and Kinnear, 1956), and polymyositis (Bloch and others, 1965).

The first purpose of this investigation was to determine the prevalence of Sjögren's syndrome in patients suffering from proven pernicious anaemia.

In idiopathic Addison's disease there is atrophy of both adrenal cortices with loss of most of the cortical cells, lymphocytic and plasma cell infiltration, and minimal fibrosis. Chronic thyroiditis, which demonstrates similar histological changes, is present in approximately 50 per cent. of patients with idiopathic Addison's disease examined *post mortem* (Wells, 1930; Sloper, 1953; Bloodworth, Kirkendall, and Carr, 1954). Primary myxoedema has occurred with idiopathic Addison's disease with sufficient frequency to warrant the term Schmidt's syndrome (Schmidt, 1926). In addition, the chronic thyroiditis found in idiopathic Addison's disease is associated with thyroid microsomal antibodies in about 30 per cent. of the patients studied (Blizzard and Kyle, 1963; Irvine,

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1963a) and thus is probably of the autoimmune type. Pernicious anaemia has been reported in idiopathic Addison's disease (Blizzard and Kyle, 1963; Irvine, 1963b; Kra and Barile, 1964). Gastric mucosal biopsies reveal a high incidence of chronic gastritis in patients with idiopathic Addison's disease (Feyrter and Klima, 1952; Smith, Delamore, and Williams, 1961). In addition, gastric parietal cell antibodies are more prevalent in idiopathic Addison's disease than in tuberculous cases (Irvine, 1963b). There is, therefore, strong evidence, clinical, histological, and immunological, pointing to an association between idiopathic Addison's disease, chronic thyroiditis, and chronic gastritis (which predisposes to pernicious anaemia).

Antibodies to salivary duct epithelium have been reported in patients with idiopathic Addison's disease (Blizzard and Kyle, 1963) and similar antibodies have been detected in patients with Sjögren's disease (Bertram and Halberg, 1964; Halberg, Bertram, Söborg, and Nerup, 1965; MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson, 1967).

The second purpose of this investigation, therefore, was to determine the prevalence of Sjögren's syndrome in patients suffering from idiopathic Addison's disease.

Material and methods

PATIENTS

169 patients (120 female, 49 male) comprising three groups (pernicious anaemia, idiopathic Addison's disease, and hospital controls) were included in the survey (the mean age and age range are shown in Table I). All of the patients were examined for evidence of keratoconjunctivitis sicca. The patients in the first two groups had been investigated as in-patients. Together with the help of the original case records and further specific examinations, evidence of rheumatoid arthritis, thyroid disease, and salivary duct atrophy was collected. Most of the hospital control patients were attending as out-patients and were not suffering from any disease known to have an autoimmune basis.

Group I Pernicious anaemia (77 patients: 40 female, 37 male)

Four of these had rheumatoid arthritis by the American Rheumatism Association criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958). Two had Hashimoto's thyroiditis (Buchanan, Alexander, Crooks, Koutras, Wayne, Anderson, and Goudie, 1961) and one had idiopathic Addison's disease (Anderson and others, 1967). One patient had thyrotoxicosis as well as rheumatoid arthritis and another had thyrotoxicosis.

Group II Idiopathic Addison's disease (primary adrenal atrophy) (20 patients: 15 male, 5 female)

The diagnosis was based on the exclusion of obvious causes, *e.g.* tuberculosis for extensive and irreversible destruction of the cortex of the adrenal glands (Anderson and others, 1967), and on the detection of antibodies to adrenal cortical cells (Anderson, Goudie, Gray, and Timbury, 1957; Blizzard and Kyle, 1963; Goudie, Anderson, Gray, and Whyte, 1966).

Group III Hospital controls (72 females)

These were patients attending clinics associated with the Western and Royal Infirmaries, Glasgow. None of the variety of general medical conditions from which they suffered had any known association with pernicious anaemia, thyroid disease, or autoimmune disorders.

Table I *Keratoconjunctivitis sicca in pernicious anaemia and idiopathic Addison's disease (primary adrenal atrophy)*

Clinical groups	*No. of patients*	*Age (yrs)*		*Schirmer's test (mm. at 5 minutes)*						*Kerato-conjunctivitis sicca*	
				5		5–9		10–14			
		Mean	*Range*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Pernicious anaemia	77	62·5 ± 11·1	20–82	11	14·1	14	18·0	12	14·2	6	7·7
Addison's disease	20	36·6 ± 6	20–45	—	—	—	—	1	5·0	—	—
Hospital controls	72	51·9	31–74	5	6·9	10	13·9	6	8·3	5	6·9

METHODS

Antibodies to parietal cells

These were tested using the indirect immunofluorescence technique for the detection of gastric autoantibodies. Antigen was prepared from frozen unfixed sections of normal gastric fundal mucosa (Taylor and others, 1962).

Autoantibodies to thyroglobulin

These were tested by a precipitin test using the Ouchterlony-Elekplate technique (Anderson, Buchanan, Goudie, and Gray, 1962) and by the tanned red cell haemagglutination test using thyroglobulin-coated formalized tanned sheep red cells (Burroughs Wellcome) (Fulthorpe, Roitt, Doniach, and Couchman, 1961). Autoantibody to thyroid microsomes was measured by an immunofluorescence technique on unfixed frozen sections of thyroid slices (Holborow, Brown, Roitt, and Doniach, 1959).

Other laboratory data

Waaler-Rose, latex particle, and haemoglobin tests were recorded in the patients suffering from pernicious anaemia.

Examination for Sjögren's syndrome

Each patient underwent a complete ophthalmic examination. This included a Schirmer I tear test using standardized sterile strips developed by Halberg and Berens (Contactisol Inc., Lindenhurst, New York, U.S.A.). Patients with less than 15 mm. of wetting at 5 minutes had a Schirmer II tear test using 10 per cent. ammonia held by the patient for 5 minutes at 6 in. from the nose (Williamson, Cant, Mason, Greig, and Boyle, 1967). Keratoconjunctivitis sicca was diagnosed when the Schirmer II test gave less than 5 mm. wetting after 5 minutes and when there was strongly positive staining with the vital dye rose bengal 1 per cent., punctate or filamentary, of the conjunctivae and/or corneae.

Sialography

This was performed on four patients who gave a history of dryness of the mouth and throat and who had clinical xerostomia (Park and Mason, 1966).

Results

EXAMINATION FOR SJÖGREN'S SYNDROME

The results of the examination for keratoconjunctivitis sicca are summarized in Table I. A small number of patients in Group I (pernicious anaemia) and Group III (hospital controls) were suffering from keratoconjunctivitis sicca. Although the incidence of the ocular disease was higher in Group I than Group III the difference was not significant.

Most of the patients who demonstrated a reduced Schirmer I tear test, unprovoked by ammonia, had pernicious anaemia. The average age of the anaemia group of patients was 62·5 years, 10 years more than the hospital control patients, and this may account for the apparent fall in tear secretion in the anaemia group.

None of the patients with idiopathic Addison's disease had keratoconjunctivitis sicca.

Four of the patients with pernicious anaemia had xerostomia but normal sialograms.

Table II summarizes the principal findings in those patients who had pernicious anaemia and evidence of Sjögren's syndrome.

Table II *Summary of findings in patients with pernicious anaemia, keratoconjunctivitis sicca, and/or xerostomia*

Patient no.	*Pernicious anaemia*	*Kerato-conjunctivitis sicca*	*Xerostomia*	*Rheumatoid arthritis*	*Hashimoto's thyroiditis*	*Idiopathic Addison's disease*
1	+	+	0	+	0	0
2	+	+	+	0	+	0
3	+	+	0	0	+	+
4	+	+	+	0	0	0
5	+	+	0	0	0	0
6	+	+	0	0	0	0
7	+	0	+	0	0	0
8	+	0	+	0	0	0

The first four patients listed (Table II) had evidence of involvement of other diseases. Patient 1 had rheumatoid arthritis, patient 2 xerostomia and Hashimoto's thyroiditis, patient 3 Hashimoto's thyroiditis and idiopathic Addison's disease, and patient 4 xerostomia.

Three other patients had pernicious anaemia and rheumatoid arthritis but no evidence of keratoconjunctivitis sicca. One of the patients with pernicious anaemia and rheumatoid arthritis also suffered from thyrotoxicosis.

OTHER INVESTIGATIONS

A family history of pernicious anaemia was obtained from fourteen (18·2 per cent.) of the 77 patients suffering from this disease and a history of thyroid disorders in eight (10·4 per cent.).

There was no history of pernicious anaemia or thyroid disease in the families of those suffering from idiopathic Addison's disease.

25 (32·4 per cent.) of the 77 patients with pernicious anaemia had palpable thyroid glands. In twenty patients the glands were soft, in five firm. Two of the firm glands lay beneath operation scars, one for thyrotoxicosis, the other for Hashimoto's thyroiditis. Five of the patients with pernicious anaemia had proven thyroid disease; two had Hashimoto's thyroiditis, two thyrotoxicosis, and one primary myxoedema.

LABORATORY DATA

All of the patients with pernicious anaemia were receiving Cytamen injections, the mean current haemoglobin being 11·5 ± 2·1 g./100 ml.

Antibody to gastric parietal cells was detected in the sera of 35 (77 per cent.) of 46 patients, antibodies to thyroid microsomes in eighteen (39 per cent.) of 46 patients, and tanned red cell titres were positive in thirteen (28 per cent.) of 46 patients suffering from pernicious anaemia.

Discussion

This study shows no increased prevalance of keratoconjunctivitis sicca in patients suffering from pernicious anaemia (Table I). The prevalence is higher than in Sjögren's series (Sjögren, 1933), in which his nineteen patients were distributed among 36,000 hospital patients (0·05 per cent.), and in the ophthalmic control series of de Roetth (1945) in which he found 0·2 per cent. of 6,200 patients with keratoconjunctivitis sicca. However, in neither series was the age and sex distribution recorded. The number of patients suffering from proven autoimmune thyroid disease who develop keratoconjunctivitis sicca is also no higher than in a hospital control group (Williamson and others, 1967). In the present series, it is interesting to observe that two of the six patients with pernicious anaemia and keratoconjunctivitis sicca also had autoimmune thyroiditis—Hashimoto's disease (Table II)—and that one of them in addition had idiopathic Addison's disease. However, it is accepted that a patient with any one organ-specific disease has a higher than normal tendency to develop another organ-specific disorder (Anderson and others, 1967). In Sjögren's syndrome there are organ-specific features in that there is specific destruction of the lacrimal and salivary glands. Nevertheless, a non-organ-specific connective tissue disorder, usually rheumatoid arthritis, is present in over 50 per cent. of patients with Sjögren's syndrome (Bloch and others, 1965). In this series one of the pernicious anaemia patients who had keratoconjunctivitis sicca was also suffering from rheumatoid arthritis. Three others with rheumatoid arthritis and pernicious anaemia did not have Sjögren's syndrome.

The number of patients with xerostomia was no higher than in the hospital control group reported previously (Williamson and others, 1967).

No cases of Sjögren's syndrome were detected among the twenty patients who had a primary diagnosis of idiopathic Addison's disease. Their mean age (36·6 years) is, however, much younger than either the pernicious anaemia group or the hospital control group. One patient in the pernicious anaemia series who had idiopathic Addison's disease and keratoconjunctivitis sicca has been discussed already.

The prevalence of gastric parietal cell antibodies and thyroglobulin antibodies, however, is increased in Sjögren's syndrome (Buchanan and others, 1966; Anderson and others, 1961; Bloch and others, 1965). Both of these antibodies occur with increased frequency in pernicious anaemia (Irvine and others, 1962; Markson and Moore, 1962; Taylor and others, 1962; Irvine, 1963a; Doniach and others, 1963) and in idiopathic Addison's disease (Blizzard and Kyle, 1963; Irvine, 1963b). Thyroglobulin antibodies are more frequent in the connective tissue diseases rheumatoid arthritis (Anderson and others, 1961; Bloch and others, 1965) and systemic lupus erythematosus (Anderson and others, 1961; Hijmans, Doniach, Roitt, and Holborow, 1961), both of which may be associated with established keratoconjunctivitis sicca. The absence of an increased prevalence of keratoconjunctivitis sicca in pernicious anaemia or in idiopathic Addison's disease in contrast to that in autoimmune systemic disorders is consistent, however, with the concept that pernicious anaemia and idiopathic Addison's disease are organ-specific disorders.

Summary

77 patients with pernicious anaemia and twenty with idiopathic Addison's disease were examined for keratoconjunctivitis sicca by Schirmer tear tests, staining of the conjunctiva and cornea by rose bengal dye, and slit-lamp examination. The prevalence of keratoconjunctivitis sicca in these patients was no higher than in 72 hospital controls. Sialography was performed on four patients who had xerostomia but no abnormalities were detected.

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Electronystagmographic studies of small vertical fixation movements

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Statistical estimates of the accuracy with which electronystagmography (ENG) can provide eye movement records have been published by Shackel (1960). His data described horizontal eye movements over a fairly large displacement, as did data from trials comparing this technique with eye movement films described by Hoffman, Wellman, and Carmichael (1939) and Michael and Melvill Jones (1966). Elsewhere, Shackel and Davis (1960) demonstrated that monocular vertical potentials were only about 60 per cent. of the magnitude of binocular horizontal potentials, which inferred that a vertical eye movement may yield a signal with a poorer signal-to-noise ratio than a comparable horizontal one. In the opinion of Miles (1939), who presented no supporting data, this vertical potential may possibly be enlarged if the eyes are closed. Vertical fixation movements could still be particularly difficult to measure accurately, however, because of an eyelid artefact which can confuse the vertical eye movement record (Barry and Melvill Jones, 1965).

The aim of the present investigation was to perform a test-retest reliability examination of ENG records, when such records were made from small vertical eye movements. A comparison between the eye open – eye closed case was also included.

Subjects

32 subjects participated, nine of them female. Most had normal binocular visual acuity, none poorer than 6/12 corrected (as tested by the Snellen chart). None had any visible or known eye abnormality. Their ages ranged from 17·4 to 50·3 years, but only eight were in fact over 30 years old. All were known to the experimenter and none was unduly anxious about the experimental situation, as far as could be seen.

Equipment

ENG signals were obtained from suction-cup electrodes (described by Shackel, 1958) and delivered to d.c. amplification equipment. This equipment was of high input impedance (differential input) and low drift, and had gains, available by switching, from ×1,000 to ×10,000. The output was −3db down at 6 Hz, and −44db at 50 Hz. (A secondary output, flat to 60 Hz, could be introduced as an occasional check that such steep filtering was not misleading.) The amplified signals were delivered to an ultra-violet trace recorder.

Procedure

The subjects were taken individually from their laboratories or offices (each supplied with an officially-maintained lighting level), and allowed to adapt to the (normal) laboratory illumination level for 10 to 12 minutes. During this time, a small area above and below the non-preferred eye (for the cup electrodes) and a larger area on the ipsilateral volar forearm (for the earth electrode

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plate) were cleaned with alcohol (dilute, 90 per cent. BP) and abraded with electrode jelly ("Cardioluxe") on a gauze swab. The cup electrodes were placed about 1·8 in. apart, as facial structure allowed, to be symmetrically above and below the iris when the eye was in the straightforward position. After a brief equipment demonstration, the subjects were encouraged to relax.

Each subject was then seated, the head position being maintained by a rubber-covered metal browrest, and was informed that the experiment would be finished within 2 minutes. The experimenter asked each subject to close the non-preferred eye and then to touch the closed lid lightly over the corneal apex with the index finger of the ipsilateral hand. This procedure was repeated three or four times, by way of practice, and was aimed at reducing eyelid tremor to negligible proportions, without recourse to the use of adhesive tape (which figures in the technique of Aschan, Bergstedt, and Stahle, 1956). Two fixation marks subtending 8° vertically on the rough-textured white wall normal to the subject's line of gaze were named "Top" and "Bottom" fixation points. Working illumination (290–350 lux at worktop height) was provided by fluorescent units. No additional check was made on fixation accuracy.

A small experimental design randomly assigned sixteen subjects to the experimental schedule:

Both eyes open – non-preferred eye closed – both eyes open

The other sixteen followed the complementary schedule:

Closed – open – closed

5 + 10 + 5 angular changes of 8° (as per the schedule) were then recorded per subject. Fixation changes were requested verbally, at the rate of one per 1·5 seconds or so, using the simple command Top ... bottom ... top ... bottom ... etc. If the entire sequence of twenty fixations was not completed in 45 seconds, it was repeated, in an attempt to avoid spontaneous changes in ocular potential magnitude which occur over time (see, for example, Byford, 1964) and in response to illumination changes (Miles, 1940; Kris, 1958; Arden and Kelsey, 1962).

Results

Limited pre-tests showed that securing the closed lid with the index finger did apparently abolish tremor, and introduced a d.c. level shift without apparently affecting the potential output for a given angular eye movement.

Best fit straight lines were drawn through each individual fixation record, disregarding the alternate records which might normally be used to assess equipotential lines more reliably. The upper trace in the Figure makes this clear. The separation on the record was then measured for each fixation, taking any axis drift into account. These measurements could then be compared in magnitude with a 100 μV calibration signal recorded from a square-wave generator.

The small eyelid artefact associated with an upward movement (lower record in the Figure, peaks at the left end of each upper fixation line) is typical of this subject. Some

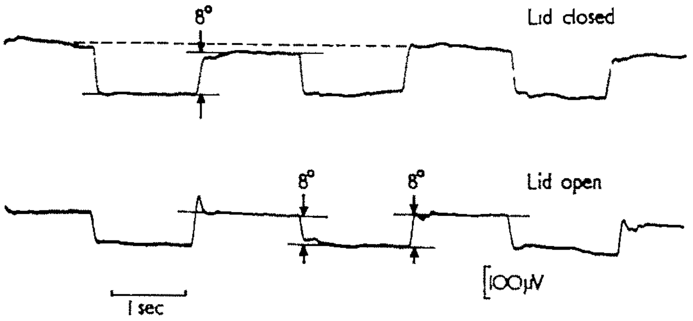

FIGURE *Example electronystagmographic records, showing method of measurement. Upper record represents fixations with the eye closed* subjects appear to produce nearly no artefact, others a large pulse, but consistency was not systematically studied.

It was then possible to calculate, for each subject, the mean ENG potential (in µV) produced by the ten fixations with the eye open and by the ten fixations with the eye closed. The ratio µV open/µV closed could then be computed for each subject. Overall, there was no difference between the two conditions (as shown by the Wilcoxon T statistical test: Siegel, 1956).

Using only the ten fixations forming the continuous centre section of each subject's experimental schedule, coefficients of variation could be calculated. These express the scatter (standard deviation) of the fixation record amplitudes as a percentage of the mean amplitude. The sixteen coefficients describing record variability with the eye closed were not different from the sixteen with the eye open (as shown by the Mann-Whitney U statistical test: Siegel 1956), and could therefore be pooled. This confirms the observation that inconsistencies such as that illustrated in the top trace of the Figure occur equally with the eye open and with the eye closed.

The results are given in Table I. Distributions were apparently normal for all three data sets, but the data population is, of course, too small to permit a statistical test of this.

Table I *Electronystagmography. Reliability and potential magnitude data*

Measurement	*Mean*	*Median*	*Range*
Potential (µV/8°) eye open	96	87	38–189
Potential ratio $\frac{\mu V \text{ eye open}}{\mu V \text{ eye closed}}$	1·09	·97	·4–2·1
Coefficient of variation $\frac{100 \text{ S.D.}}{\text{Mean}}$	11·20	10·70	4·8–23·7

Note: A high coefficient indicates unreliability

Using the Wilcoxon T statistic (two tails) it was shown that the group of 32 subjects could be analysed as in Table II.

Table II *Potential magnitude, comparing eye open and eye closed, for 32 subjects*

Greater potential for eye open			*No difference*	*Greater potential for eye closed*		
P< ·01	P< ·02	P< ·05		P< ·05	P< ·02	P< ·01
11	0	2	7	1	2	9

This breakdown was independent of experimental schedule.

Spearman rank order correlations (as described by Siegel, 1956) were used to confirm ($P < \cdot 01$; $r_s = 0{\cdot}503$) that larger potential magnitudes permitted greater reliability of measurement. It was further confirmed that age is no useful predictor of ocular potential magnitude ($r_s = -0{\cdot}114$, insignificant: Shackel, 1967, mentions his own and others' work leading to the same conclusion). Nor was age related to the potential ratio µV open/µV closed ($r_s = -0{\cdot}091$, insignificant). Tests using the Mann-Whitney U statistic (Siegel, 1956) showed that the older sixteen subjects (containing all ten with less than normal visual acuity) were insignificantly different from the younger sixteen subjects in terms of the parameters in Table I.

Discussion

When a random sample of the general population is required for accurate ENG recording, ENG potential magnitude, and hence record measurement accuracy will not be improved by the closure of the eye. Individuals may be selected from the population, however, for a potential reliably greater for either the eye open or the eye closed case.

The eyelid movement artefact which can confuse ENG records from the vertical axis can, of course, be suppressed by closing the eye. Requesting individuals to touch the closed lid of their non-preferred eye eliminates the artefacts due to lid tremor without confounding the ENG record.

In the more reliable 68 per cent. (mean ±1 SD) of an average, short record (less than 45 sec.) the eye yields an ENG signal representing anything from 7·1° to 8·9° from an initial locus for a requested rotation of 8·0°. The error can be in excess of 3·5° for a few individuals, however. Little of this can be referable to the normal eye movements of fixation (Ditchburn and Foley-Fisher, 1967), although some may be due to inaccurate fixation. Outside this more reliable data, very large errors are occasionally seen which are surely not due to faulty fixation, but more likely to the vagaries of the ocular potential. Casual inspection of the records suggests that errors operate randomly, such that the arithmetical average of ten to twenty measurements might be expected to be highly reliable indeed.

Summary

Electronystagmographic (ENG) records were taken from 32 individuals required to perform 8° vertical fixations. Estimates were made of ENG record reliability. Closing the eye eliminates any eyelid movement artefact, of course, but does not generally affect the ENG potential level which goes to determine record measurement accuracy.

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Occlusion therapy in amblyopia with eccentric fixation

Comparison of conventional, non-conventional (inverse), and red-filter occlusion

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Occlusion of the sound eye (conventional occlusion) introduced by Buffon (1743) was the only treatment for amblyopia until Bangerter (1953) introduced occlusion of the amblyopic eye (non-conventional or inverse occlusion) combined with pleoptic treatment in cases of amblyopia with eccentric fixation. Mackensen, Kröner, and Postić (1965), von Noorden (1965), Postić (1966), Borgmann and Dielefeld (1967), and Ver Lee and Iacobucci (1967) found conventional occlusion of the sound eye to be as good as pleoptic treatment. On the other hand, Arruga (1962) and Cibis and Windsor (1967) favoured non-conventional (inverse) occlusion of the amblyopic eye. Brinker and Katz (1963) introduced red-filter occlusion to avoid the shortcomings of pleoptic treatment.

Because of the disparity in the results given by various authors, the present study was undertaken to provide comparative data and to ascertain the significance of such factors as age of patient, fixation pattern, refractive error, and strabismus in the response to occlusion therapy. This study includes a number of patients above the age of 12 years—a group not discussed by other workers.

Material and methods

Seventy cases of amblyopia with eccentric fixation but no other ocular abnormality were selected for occlusion therapy. Pleoptics were not combined with any of the occlusion methods. The diagnosis of eccentric fixation was established and the degree of eccentric fixation determined by using the Linksz star graticule in Keeler's projectoscope. A distinction was made between eccentric fixation and eccentric viewing, and only cases with true eccentric fixation were included in this series. The eccentricity was graded according to the classification of Malik, Gupta, and Choudhry (1969). Visual acuity was measured by using Snellen's "Whole line optotypes".

The cases were divided into three groups:

Group I (18 cases) Conventional occlusion (of the unaffected eye)

Group II (24 cases) Non-conventional occlusion (of the affected eye)

Group III (28 cases) Red-filter occlusion (of the affected eye).

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Only one type of occlusion was used for each case. Each group was analysed by the following clinical features:

(*a*) *Age of patient:* 3 to 6, 7 to 9, 10 to 12, and above 12 years

(*b*) *Type of eccentric fixation*

(*c*) *Degree of refractive error*

(*d*) *Type and degree of strabismus*

Conventional and non-conventional occlusion was carried out by Doyne's occluder, taking care that no light entered the occluded eye; the occlusion was applied throughout the patient's waking hours.

Red-filter occlusion was carried out by the method described by Malik, Gupta, Choudhry, and Sen (1968a).

The patients were examined every fortnight to assess the improvement in visual acuity and fixation. The duration of treatment ranged from 6 to 30 weeks.

Observations

These are summarized in Tables I to IV.

The response to all types of occlusion was better in patients with less dense initial amblyopia and with eccentric fixation close to the fovea. With conventional occlusion 83·3 per cent. of cases showed improvement, and with non-conventional occlusion the results were relatively poor (33·3 per cent.).

Table I *Response of visual acuity to various methods of occlusion, by age group*

Age Group (yrs)	*Conventional*		*Non-conventional*		*Red-filter*	
	Same	*Improved*	*Same*	*Improved*	*Same*	*Improved*
3–6	1	5	3	–	—	2
7–9	1	–	2	–	1	3
10–12	–	2	2	1	2	1
Above 12	1	8	11	5	10	9
Total	3	15	18	6	13	15

Table II *Response of fixation to various methods of occlusion, by age group*

Age Group (yrs)	*Conventional*		*Non-conventional*		*Red-filter*	
	Same	*Improved*	*Same*	*Improved*	*Same*	*Improved*
3–6	3	3	2	1	1	1
7–9	1	–	1	1	1	3
10–12	–	2	2	1	1	2
Above 12	4	5	13	3	11	8
Total	8	10	18	6	14	14

Table III *Overall improvement obtained by various methods of occlusion*

Type of occlusion	*Total cases*	*Improvement*					
		Visual acuity		*Fixation*		*Total*	
		No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Conventional	18	15	83·3	10	55·5	15	83·3
Non-conventional	24	6	25·0	6	25·0	8	33·3
Red-filter	28	15	53·6	14	50·0	16	57·1

Table IV *Degree of refractive error related to overall improvement, by various methods of occlusion*

Type of occlusion	*Degree of refractive error (dioptres)*							
	0·50–2		2·25–4		4·25–6		*More than* 6	
	Same	*Improved*	*Same*	*Improved*	*Same*	*Improved*	*Same*	*Improved*
Conventional	1	4	1	7	1	2	–	2
Non-conventional	4	2	5	4	1	2	6	–
Red-filter	5	7	3	6	1	1	3	2

Discussion

CONVENTIONAL OCCLUSION This gave the best results, especially with regard to improvement in visual acuity. The fixation pattern of the amblyopic eye and the density of the initial amblyopia were found to be more important than the age of the patient. Improvement was not related to the refractive error or to the presence or absence of strabismus.

Our results in cases of parafoveal fixation compare well with those of von Noorden (1965), who obtained improvement in 81·8 per cent. of patients with similar degrees of eccentric fixation, but von Noorden also had good results in cases with paramacular and peripheral fixation (91·6 and 90·6 per cent. respectively). We were unable to collect enough cases of this type of fixation suitable for conventional occlusion to make a strictly valid comparison, because most of our patients were older and needed to use the sound eye for their work. But our results agree with those of many other workers who have found that amblyopia with eccentric fixation can be improved by conventional occlusion: Scully (1961) 98·2 per cent.; Sternberg and Bohár (1961) 80 per cent.; Little and Ogilvie (1963) 75 per cent.; Mackensen and others (1965) 90 per cent.; von Noorden (1965) 93·4 per cent.; Catford (1967) 89·4 per cent. In almost all these reports the patients were under 12 years of age, but we found a good response to conventional occlusion in patients over 12 years old provided that the fixation was close to the fovea.

NON-CONVENTIONAL OCCLUSION Our results were poor as regards both fixation and visual acuity. This was true for all age groups and all types of fixation, although cases of erratic and parafoveal fixation showed better results than cases of peripheral fixation. The apparently better response of cases without manifest strabismus was due to the fact that these included more cases of erratic and parafoveal fixation.

Our 33·6 per cent. improvement in this group may be compared with those of von Noorden (1965) 34·5 per cent., Andrée (1966) 25·0 per cent., and Malik and others (1968a) 30·8 per cent., but differs widely from those of Arruga (1962) 93·0 per cent. and Cibis and Windsor (1967) 70·0 per cent. This discrepancy could be due to the fact that almost all Arruga's patients were under 4 years of age.

RED-FILTER OCCLUSION This gave encouraging results in both fixation and visual acuity. The response was better in patients under 12 years old (77·7 per cent. improved) than in those over 12 years old (47·4 per cent. improved).

The results were good in cases of erratic and parafoveal fixation (100 and 62·5 per cent.) irrespective of the age of the patient.

We have previously reported better results in patients with small degrees of eccentric fixation (Malik, Sood, Gupta, and Choudhry, 1968b) but only three of nine cases with paramacular fixation and one of four cases with more peripheral fixation (*i.e.* paracaecal and centrocaecal) showed improvement. This observation is contrary to the findings of most other workers who obtained excellent results even in cases of grossly eccentric fixation (Brinker and Katz, 1963; Binder, Engel, Ede, and Loon, 1963; von Noorden, 1965; Cowle, Kunst, and Philpotts, 1967). This disparity may be explained by the assumption that the other workers were treating younger patients (under 11 years) in whom the eccentric point is still in a stage of flux and more amenable to treatment. In our series, only one of two patients with paramacular fixation below 12 years of age showed improvement, and the one patient with peripheral fixation who improved was only 6 years old.

The response to red-filter occlusion was much better in cases with less than 4 dioptres of refractive error. This was related to the fixation pattern also; of eight patients with parafoveal fixation, five improved and the other three had a refractive error of more than 4 dioptres.

The presence or degree of strabismus had no prognostic effect on red-filter treatment (Table V).

Table V *Strabismus related to overall improvement, by method of occlusion*

Strabismus	*Conventional*		*Non-conventional*		*Red-filter*	
	Same	*Improved*	*Same*	*Improved*	*Same*	*Improved*
Absent	1	3	4	3	2	5
Unilateral Up to 15°	2	11	7	3	7	8
15–30°	–	1	4	2	3	2
Alternating Up to 15°	–	—	—	–	—	1
15 to 30°	–	—	1	–	—	—
Total	3	15	16	8	12	16

Summary

Seventy cases of amblyopia with eccentric fixation have been treated by conventional, non-conventional, and red-filter occlusion and the results have been assessed in relation to age of patient, fixation pattern, refractive error, and strabismus. Conventional and red-filter occlusion were better than non-conventional occlusion. The first improved both visual acuity and fixation and the second improved fixation. Patients with erratic

and parafoveal fixation had a good prognosis regardless of their age. Refractive errors of more than 4 dioptres, even in younger patients with fixation close to the fovea, carry a poor prognosis with red-filter occlusion. The presence or absence of strabismus had little prognostic significance.

It is concluded that, wherever feasible, conventional occlusion should be tried first, especially in children. If it is not possible to get the co-operation of the patient for full-time occlusion of the sound eye because of dense amblyopia, red-filter occlusion may be used. Non-conventional occlusion is not of much therapeutic value unless it is combined with intensive pleoptic treatment.

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Strengthening the sclera with a strip of fascia lata in progressive myopia

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The surgical methods of treating myopia may be divided into two groups:

(1) Removal of the clear lens (Fukala, 1890), operations on the cornea to reduce its refractive power (Sato, Akiyama, and Shibata, 1953), lamellar resection of the sclera, implantation of an intraocular lens (Choyce, 1964).

These operations decrease the degree of myopia but do not check its progress.

(2) Operations which disrupt the pathogenetic mechanism responsible for the progress of the myopia by supporting the posterior segment of the sclera with auto- or homotransplants. Strips of tendon (Malbrán, 1954), of sclera (Borley and Snyder, 1958; Miller and Borley, 1964), or of fascia lata (Shevelev, 1930; Curtin, 1961) are used for this purpose and good results have been reported. There is no further stretching of the globe and visual acuity improves.

The reduction of myopia usually reported is probably due to the postoperative contraction of the transplant and sclera.

In our opinion the procedure of strengthening the sclera with fascia lata offers the best prognosis. Fascia tissue is not only more elastic than either sclera or tendon, easy to handle, and sufficiently strong (Curtin, 1960), but can also be taken from the patient himself.

The method of supporting the posterior sclera with a strip of fascia lata was worked out experimentally by Shevelev (1930). Later Curtin (1960, 1961) described a similar operation which he had performed successfully on seven subjects with progressive myopia. Eroshevsky (1968) has reported favourably on the results of Curtin's operation which he has performed on twenty eyes.

We have simplified and improved the Shevelev-Curtin operation. A description of the technique and a report on the results in 84 eyes of 67 patients form the subject of the present communication.

Surgical technique

INSTRUMENTS

Along with the conventional instruments we use a special fascial stripper to dissect the strip of fascia and a hooked carrier to pass the fascia behind the globe (Fig. 1, opposite).

The stripper consists of two tubes, one inside the other. The outer tube (170 mm. long, outer diameter 8 mm., inner diameter 6 mm.) has a handle at one end, and the other end is tapered to a cone. The inner tube is the same length as the outer one, and its diameter is such that it moves freely inside it.

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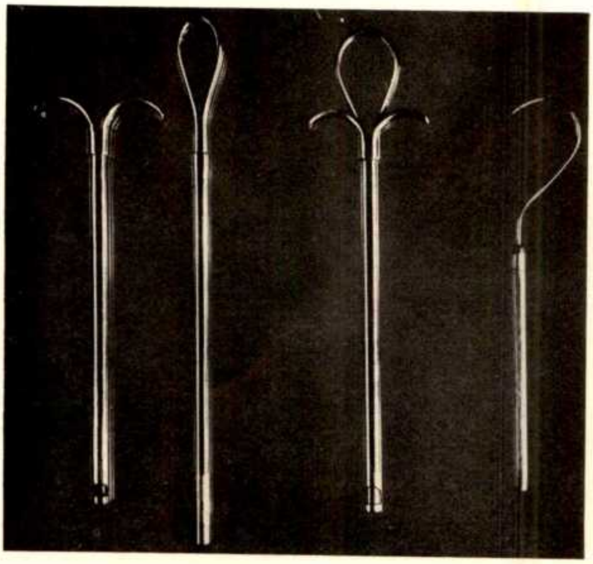

FIG. 1 *Fascial stripper and hook. Outer tube; inner tube; instrument assembled; Curtin's fascial hook*

The hook used to pass the strip of fascia behind the globe consists of a handle, an eye-shaped curve and a small eye at the end.

GRAFT

Under local anaesthesia with 0·25 per cent. solution of procaine, a 30-mm. incision of the skin is made along the dividing line between the upper and the middle third of the outer surface of the thigh. The wound is pulled apart with the hooks. Two parallel incisions of the fascia lata are made 6 mm. apart, and joined at the top by a third one. The resultant strip is passed through the lower end of the stripper and out through the aperture in the side of the outer tube, where it is gripped with a clamp. After that the stripper is moved subcutaneously towards the knee to the required length (100–120 mm.). The inner tube is inserted into the outer one and turned slightly to cut off the strip. The stripper and fascia are removed and the wound sutured.

The strip of fascia is laid on moist gauze and cut longitudinally to make a Y-shaped transplant with two narrow arms and one broad one (Fig. 2).

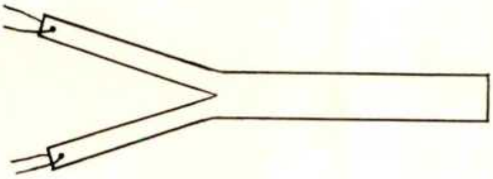

FIG. 2 *Y-shaped graft*

OPERATION

After a lateral canthotomy, a conjunctival-tenon incision about 10 mm. long is made about 7 mm. temporal to the limbus. The lateral rectus muscle is taken up in two catgut ligatures and is cut off. A traction suture is put in across the stump of the muscle tendon.

Two conjunctival-tenon incisions are made 6 mm. from the limbus in the supero-nasal and infero-nasal quadrants (Fig. 3, overleaf).

The Curtin hook is passed behind the globe from the supero-nasal incision until its end comes out through the lateral incision. This procedure is made easier by turning the eye with the help of the traction suture (Fig. 4).

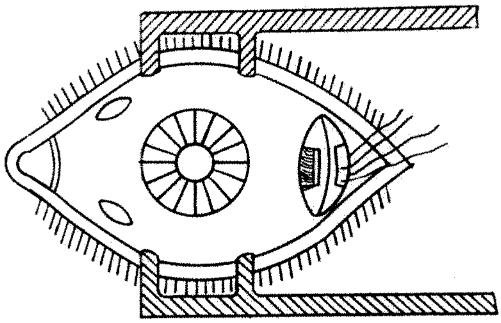

FIG. 3 *Position of conjunctival-tenon incision on the globe*

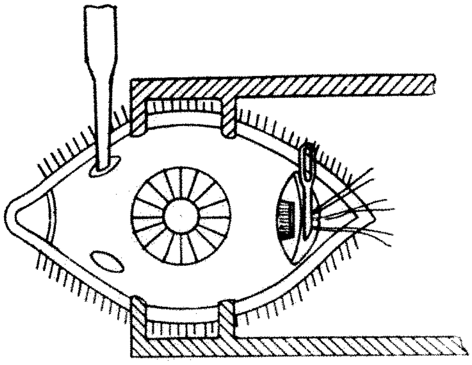

FIG. 4 *Fascial hook passed into the supero-nasal incision and out through the temporal incision*

One of the narrow transplant arms is threaded through the eye, and pulled back behind the globe. This manipulation is repeated through the infero-nasal incision and the other narrow arm is passed through. The two arms are drawn until the central part of the graft is felt to reach the optic nerve. The third broad arm now runs along the horizontal meridian at the temporal side of the eyeball (Fig. 5).

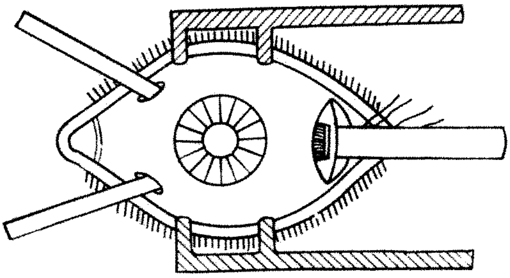

FIG. 5 *Position of the graft before suturing the ends to the sclera*

The position of the graft at the front and back of the globe is shown in Fig. 6.

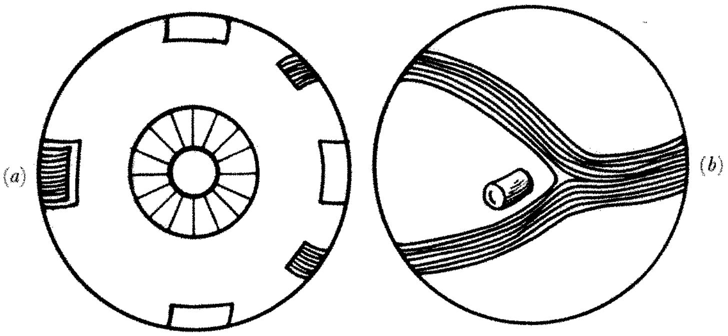

FIG. 6 *Position of transplant after operation*
(*a*) Anterior
(*b*) Posterior

Each arm is fixed to the sclera by means of two silk sutures 7 to 8 mm. from the limbus, and the superfluous ends are cut off. The lateral rectus is re-sutured to the globe, the conjunctival incisions are closed with silk (3–0), and the retina is examined with the ophthalmoscope to make sure that the blood circulation is not impaired.

We originally used an X-shaped graft according to the method of Shevelev (1930) and Curtin (1960, 1961), but in cases of high myopia with an egg-shaped eyeball it is difficult to keep the graft in the correct position. When the arms are drawn tight they tend to slip from the oblique to the vertical meridian so that the centre comes away from the posterior pole. This not only reduces the effect of the operation but may block the vortex veins. The Y-shaped graft will support the sclera just where it is most stretched along the horizontal meridian.

Results

84 operations were performed in 67 patients, both eyes being operated upon in seventeen patients. The age of the patients varied from 8 to 52 years, and the myopia from 10 to 39 D sph. (mean 14 D). 23 eyes were astigmatic (more than 1 D cyl.). Sixteen patients (23 eyes) had degenerative changes of the choroid and retina. One female patient showed advanced pigmentary degeneration of the retina. The myopia was progressive in every case.

Complications

There were no operative complications. After the operation all the patients had tenonitis, manifested by oedema of the conjunctiva and eyelids, mild proptosis, and some discomfort on moving the eye. These phenomena were less marked if a tight bandage had been used postoperatively. The tenonitis disappeared in 3 to 4 days.

One female patient (myopia 24 D) developed retinal detachment on the 17th day after the operation, which may have been due to physical strain (the patient was waxing floors). One year after the operation the visual acuity was 0·05 above the initial figure and the myopia had decreased by 5 D.*

Visual acuity

The immediate postoperative results were as follows. An improvement in visual acuity and myopia was observed in 82 out of 84 eyes. Before the operation the visual acuity varied from 0·005 to 0·1 (0·01 to 0·5 with correction) and after the operation from 0·02 to 0·3 (0·06 to 1 with correction). The average improvement was 0·03 to 0·14 (0·22 to 0·35 with correction).

The power of corrective glasses decreased by 1 to 8 D (average 3·6). Sciascopic myopia decreased by 1 to 8 D (average 3·6 D).

Follow-up

Twenty eyes have been under observation for from 3 to 12 months, 48 from 12 to 24 months, and sixteen from 24 to 37 months. In the 64 eyes which have been followed up for more than a year only slight changes have been noted. The visual acuity rose in fourteen more eyes, did not change in 45, and decreased in five. The degree of myopia increased slightly in four eyes, but did not reach the preoperative level.

The required power of corrective glasses continued to decrease in 31 and remained unchanged in 33 eyes. The degree of myopia has now decreased by an average 0·47 D compared with the immediate results.

The corrected visual acuity increased in eighteen eyes, did not change in 44, and decreased (by 0·02–0·04) in two subjects with degenerative changes of the central retina and choroid. The corrected visual acuity has now risen by an average of 0·04 compared with the immediate results.

There has been no material change in the twenty eyes observed for up to one year (3 to 12 months).

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*When X-shaped grafts were used three patients had more serious complications (Nesterov and Libenson, 1967).

Illustrative case

A woman aged 36 years had bilateral progressive myopia. The visual acuity was 0·06 in the right eye (0·2 with −13 D sph.) and 0·01 in the left eye (0·05 with −14 D sph.). Numerous atrophic chorio-retinal foci were present in the macular and paramacular regions of the left eye.

The operation was first performed on the worse (left) eye, and there was moderate postoperative tenonitis for 5 days. The visual acuity improved to 0·06 (0·2 with −11 D) 3 weeks after the operation. One year after the operation the visual acuity was 0·06 (0·25 with −10 D); 33 months after surgery there were no further changes in either vision or refraction. The right eye was then operated upon. There were no complications either during the operation or postoperatively, and after 3 weeks the visual acuity improved to 0·3, but the degree of sciascopic myopia was unchanged at 13 D. In the course of 28 months the visual acuity improved to 0·2 (0·4 with −9 D).

Summary

A method of strengthening the sclera with fascia lata in cases of progressive high myopia is described. The advantages are the simplified technique, the lessened risk of blocking the vortex veins, and the strengthening of the sclera along the horizontal meridian of the eye.

The findings are reported in 84 operations on 67 patients with myopia ranging from 10 to 39 D. There were no operative complications, and the visual acuity improved in all but two cases. After prolonged follow-up no increase in the myopia has been observed.

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Prognostic value of the electroretinogram in severe recent ocular trauma

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In patients suffering from severe recent ocular trauma it is important to know the extent of the retinal damage before assessing the possible recovery of visual function. Ophthalmoscopic examination of the fundus is often impossible because of opacities of the ocular media caused by the trauma. In such cases the electroretinogram (ERG) is of value in assessing the state of the retina, but very few electrophysiological investigations have so far been published on such cases. This is probably because there are various technical difficulties in recording the ERG in these patients. An attempt has been made in our laboratory to overcome these difficulties.

The present paper analyses the ERGs recorded in 61 eyes in which severe and recent (less than 2 months) trauma had rendered the fundus invisible. In nineteen eyes the first record of the ERG was made during the first 5 days after the trauma, and in the rest between the sixth and the sixtieth day. This was because most of the patients had first been treated in other hospitals and later referred to our laboratory.

These 61 eyes had sustained perforating wounds, intraocular foreign bodies, or severe contusions (Table); all foreign bodies were extracted during the first 20 days after the injury.

Table *Analysis of* 61 *cases,* 32 *of which were followed long enough for the final visual acuity to be assessed*

Group ERG		*I Extinguished*					*II Diminished*					*III Subnormal*					*IV Normal*				
No. of cases		*	†	*Visual acuity*			*	†	*Visual acuity*			*	†	*Visual acuity*			*	†	*Visual acuity*		
		T	*F*	*A*	*B*	*C*	*T*	*F*	*A*	*B*	*C*	*T*	*F*	*A*	*B*	*C*	*T*	*F*	*A*	*B*	*C*
Trauma	Perforating wounds	6	2	2	0	0	8	6	5	1	0	10	4	1	1	2	4	2	0	0	2
	Foreign bodies	2	2	2	0	0	2	0	0	0	0	2	0	0	0	0	5	4	0	1	3
	Contusions	7	3	3	0	0	3	1	0	1	0	6	4	0	0	4	6	4	0	0	4
	Total	15	7	7	0	0	13	7	5	2	0	18	8	1	1	6	15	10	0	1	9

* *T* — Total † *F* — Followed
Visual acuity — *A* Blind; *B* 0·05–0·3; *C* Better than 0·3

Method

Three types of recording technique were used according to the technical difficulties encountered in these injured eyes.

(1) In many contusions and in most cicatrized perforating wounds it was possible to use a contact lens electrode and the standard technique of our laboratory. This method (Jayle's adapto-dynamic technique) has been described more extensively elsewhere (Jayle, Boyer, and Camo, 1959; Jayle, Boyer, and Saracco, 1965; Jayle, Tassy, and Graveline, 1968).

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The pupils are dilated. The patient is first light-adapted for 3 minutes (the adapting light is white and provides an illumination of approximately 3,000 lux at the level of the corneae). The patient is then dark-adapted for 12 minutes; during that period, responses to white, red, and blue flashes given successively at 30-second intervals are recorded. The stimulator is a Retinéclat (Alvar Electronic); we use flashes of arbitrary intensity 4 on this apparatus. These flashes are white, short (approximately 50 µsec.), and intense. The quantity of illumination measured at corneal level is approximately 5 lux.sec. and as the flashes are 50 µsec. in duration, the peak illumination on the corneae is above 100,000 lux. Red and blue flashes are obtained by using Kodak Wratten filters 26 and 47B.

Since 1964 we have added to our standard method a study of the oscillatory potential of the ERG during dark and light adaptation (Jayle and others, 1968; Tassy, 1966). The oscillatory potential is recorded in response to flashes twenty times brighter than those used in Jayle's adapto-dynamic technique. This stronger intensity was added in our laboratory to the commercially available stimulator and designated intensity 5. The ERGs are averaged by an electronic averager (CAT 400B, Mnemotron).

(2) In very severe contusions and recently-sutured perforating wounds it was impossible to use a contact lens electrode, and we therefore tested three possible substitutes:

(*a*) Small silver electrodes stuck on the skin a few millimetres from the margin of the lids. Using an averager we showed (Tassy, 1966; Tassy, Jayle, and Graveline, 1968) that these electrodes permitted not only the a- and b-waves but also the oscillatory potential to be studied.

(*b*) Cotton-wick electrodes located on the conjunctiva.

(*c*) Hook-shaped eyelid retractors (Fig. 1); these electrodes were found to be the most practical for routine work in wounded eyes. We tested several kinds of hook electrodes; the simplest hook (bottom of Fig. 1) is very light (0·2 g.) and therefore better for wounded eyes. This hook can easily be made from 0·7 mm. diameter silver wire, the tip being rounded by melting it in the flame of a Bunsen burner. The hook remains quite malleable and can be bent with the fingers so as to be

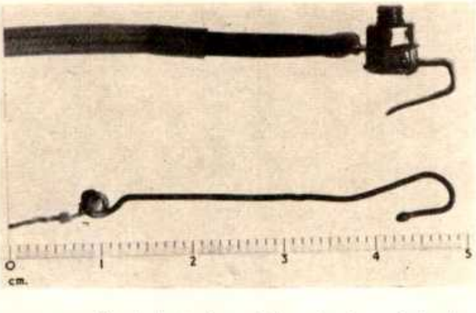

FIG. 1 *Hook-shaped eyelid retractor electrodes. The upper hook electrode is adapted from Jacobson, Uchida, and Masuda (1966). The lower hook was designed in our laboratory. Scale in centimetres*

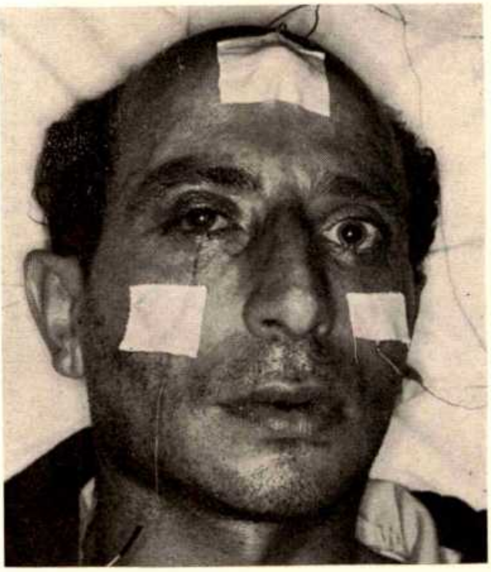

FIG. 2 *The simplest kind of hook electrodes (lower hook in Fig. 1) attached to a patient with a perforating wound of the right eye caused by a magnetic foreign body located in the vitreous. The eye showed a lacerated cataract with incorporation of lens matter in the corneal wound. The wound was sutured and the foreign body removed by the posterior route immediately after the trauma. The ERG was recorded 5 days after the trauma, while the patient was lying in bed*

fitted and secured on the lid even if it is injured and oedematous. The whole hook, except the tip, is insulated with a thin coat of nail varnish. The wire soldered to the hook electrode is glued to the cheek with adhesive plaster (Fig. 2). The hook remains in close contact with the corneal limbus, and thus enables the whole electroretinographic course of dark adaptation, as described above, to be recorded.

The responses recorded with the hook have an almost identical waveform to those obtained with contact lens electrodes (Fig. 3), and their amplitude is about 50 to 70 per cent. of that provided by the latter. The background noise is sometimes more marked with hook electrodes but does not prevent the interpretation of the records. A record with very little noise may be obtained using the averager (Fig. 3).

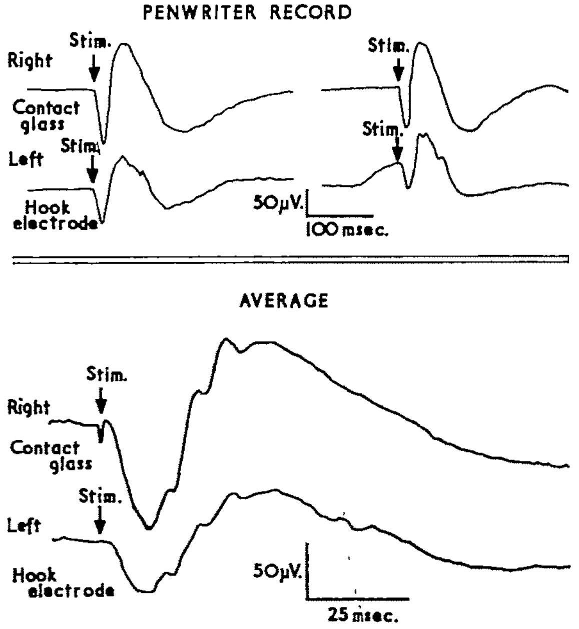

FIG. 3 *(ERG No. 4478). Comparison of ERGs recorded in a normal subject with a contact lens electrode on the right eye and a hook electrode on the left. White flashes of intensity* 4

Upper traces: penwriter records (time constant 0·3 sec.)

Lower traces: averages of twenty responses (time constant 0·5 sec.)

(3) Some patients who had not yet undergone surgery for a perforating wound or intraocular foreign body could not be moved, but the procedure could be carried out while the patient lay on a bed or stretcher. Hook or skin electrodes were used and the responses to a few white, red, and blue stimuli were recorded using flashes of intensity 4. An averaged record was made of the response to white flashes first of intensity 4 and then of intensity 5.

It was thus possible to record without risk the ERG of most traumatized eyes the day of the accident or very soon afterwards.

Results

As we used several different recording techniques we could not compare the recorded responses directly. The ERGs were therefore classified in four groups according to their amplitude measured as a percentage of the normal with each technique. This classification was made using only the responses to white flashes (the reasons for this choice will be given below in the Comments section).

In the standard Jayle's adapto-dynamic technique the normal range of amplitude was known from previous studies (Jayle and others, 1959, 1965); with the other techniques, the amplitude of the undamaged eye was taken as normal (none of these eyes were diseased).

GROUP I EXTINGUISHED (or nearly extinguished) ERGS
Reduced to less than 10 per cent. of the normal amplitude.

GROUP II GREATLY DIMINISHED ERGS
Between 10 and 50 per cent. of the normal.

GROUP III SUBNORMAL ERGS
Between 50 and 75 per cent. of the normal.

GROUP IV NORMAL ERGS
Above 75 per cent. of the normal.

The ERG was recorded less than 2 months after the trauma in 61 eyes, but only 32 of these were followed up long enough to know the final state of the visual acuity. For instance, among patients with traumatic cataracts, we considered that the final recovery was known only if the cataract had been extracted.

These 32 eyes were then classified into three groups according to the recovery of the visual acuity (see Table).

GROUP A
Visual acuity less than 0·05 or atrophic and painful eyes which had to be enucleated.

GROUP B
Visual acuity between 0·05 and 0·3.

GROUP C
Visual acuity greater than 0 3.

The prognostic value of the ERG recorded soon after the trauma was assessed by comparing the ERG classification with the visual acuity classification.

GROUP I EXTINGUISHED

Of the fifteen eyes in this group, seven were followed long enough to know the evolution of the visual acuity. All seven were placed in Group A; three had to be eviscerated or enucleated and the others had only perception of light.

Case 1 (No. 2370)

A man aged 46 years was admitted to hospital after receiving a blow with the fist on the left eye; apparently he had only a hyphaema, but he was deaf, dumb, and illiterate so that it was impossible to know whether he saw the light or not. The ERG was extinguished. 2 months later, the hyphaema was absorbed and an extensive vitreous haemorrhage was observed. 5 months after the accident the eye became atrophic and painful and had to be eviscerated (Group IA).

GROUP II GREATLY DIMINISHED

Of the thirteen eyes in this group seven were followed long enough to know the final visual function. Five did not recover any useful vision or had to be eviscerated (Group A), and the other two were classified in Group B, the final visual acuity being 0·2 and 0·3 respectively. An example of an eye in Group II A is given below.

Case 2 (No. 3652)

A man aged 43 years had his right eye pierced by a small lead shot which lodged in the ethmoid. He was admitted to a neighbouring hospital, where a severe vitreous haemorrhage was observed, and was sent to our laboratory for an ERG recording 7 days after the accident. The ERG was found to be greatly reduced (Fig. 4). 14 days after the trauma the eye appeared to be "quiet" although the fundus could not yet be seen because of a vitreous haemorrhage. Before being discharged the patient was again sent to our laboratory. The penwriter record (Fig. 4) indicated that the ERG was extinguished, but there was an ample negative wave due to a blink movement in response to each flash and this wave might conceal a small or late ERG. In fact the averaged record showed a small abnormal ERG. Because of these ERG findings a retinal detachment was suspected and the patient was kept in hospital. A week later the vitreous became clearer and examination with the Goldmann three-mirror contact lens revealed a definite retinal detachment. A sclerectomy was performed and the retina reattached. A year after the accident the retina remained attached but the ERG was extinguished and the visual acuity reduced to perception of light (Group II A).

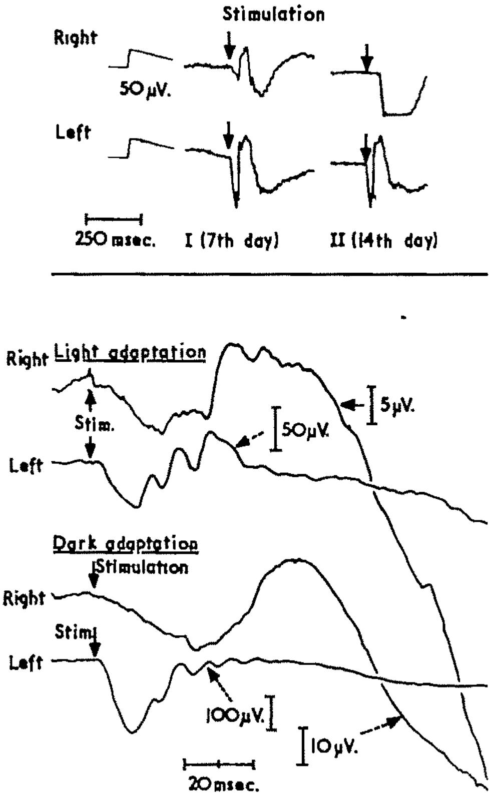

FIG. 4 *Case 2 (ERG No. 3652). Right eye pierced by a small lead shot; left eye normal*

Upper. penwriter record made with Jayle's adapto-dynamic technique 7 and 14 days after the accident. Figure shows only the responses to a white flash after 11 min dark adaptation; time constant 0 3 sec.

Lower: averaged record made 14 days after the accident, average of thirty responses to white flashes of intensity 5 after 13 min. dark adaptation; stimulation frequency 1/6 hertz, time constant 0 5 sec.

Note difference in scale between the records of the two eyes.

GROUP III SUBNORMAL

Of the eighteen eyes with subnormal ERGs during the first 2 months after trauma, eight were followed long enough to know the final visual function. One had a bad result (Group A) due to traumatic uveitis and another had a visual acuity of 0·2 (Group B) after the discission of a traumatic cataract. The other six patients regained a visual acuity greater than 0·3 (Group C); an example of these is given below.

Case 3 (No. 2745)

A girl aged 15 years had received a blow with a shoe on her left eye. There was a complete hyphaema and later an extensive vitreous haemorrhage was seen. The ERG was subnormal (Fig. 5, overleaf).

For 8 months there was partial blood-staining of the cornea and no fundus reflex because of vitreous opacities, the visual acuity being reduced to perception of light. The ocular media began to clear and a year after the accident the patient had recovered a visual acuity of 0·9; the fundus then became visible and was found to be normal (Group III C).

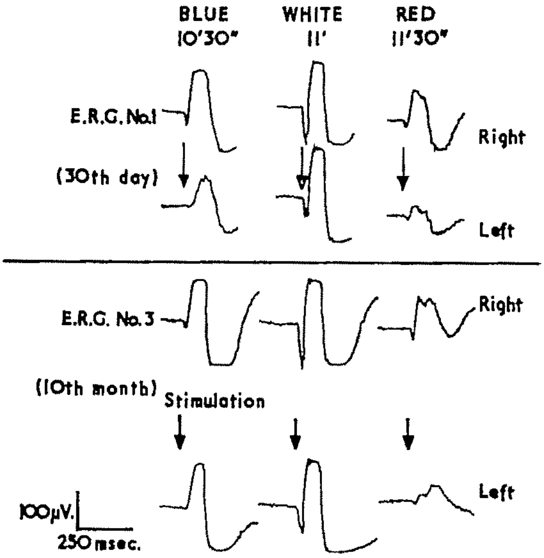

FIG. 5 *Case* 3 (*ERG No.* 2745). *Left eye severe contusion; right eye normal. Pen-writer records were made according to Jayle's adapto-dynamic technique* 30 *days and* 10 *months after the accident. The Figure shows only the ERGs recorded successively in responses to blue, white, and red flashes after* 10½ *min.*, 11 *min., and* 11½ *min. dark adaptation. Time constant* 0·3 *sec.*

GROUP IV NORMAL

Of fifteen eyes with normal ERGs, ten were followed long enough to know the final visual function. Nine of the ten had a good result (Group C). One eye (see case note No. 2404) recovered only a visual acuity of 0·3 (Group B) because of a late retinal detachment which a repeated ERG helped to diagnose.

Case 4 (No. 2404)

A man aged 59 had a magnetic foreign body in the vitreous, which was removed by the posterior route. A traumatic cataract was developing, and the first ERG recorded 17 days after the accident was within normal limits (Fig. 6), but one week later the ERG was found to be greatly diminished, and it was suspected that a retinal detachment was probably concealed by the opaque lens. After

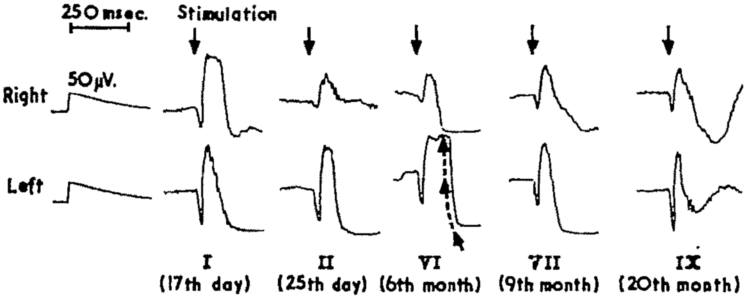

FIG. 6 *Case* 4 (*ERG No.* 2404). *Right eye magnetic foreign body removed; left eye normal. Nine records were made between the* 17*th day and the* 20*th month after the accident. Figure shows only the responses to a white flash after* 11 *min. dark adaptation (penwriter record: Jayle's adapto-dynamic technique). The sixth record is distorted by a sudden upward deflection (arrows) caused by lid movement*

full mydriasis it was possible to see a localized peripheral retinal detachment, and this and the cataract were treated surgically; 20 months after the accident the retina was still reattached and the visual acuity was 0·3 (Group IV B).

Comments

Eyes with an extinguished or nearly extinguished ERG (Group I) did not recover any useful vision. Therefore, when for clinical reasons a sympathetic ophthalmitis is feared, an extinguished ERG is a further justification for early enucleation.

Eyes with normal ERGs (Group IV) almost always achieved a good recovery of vision, even after very severe trauma. Eyes with subnormal ERGs (Group III) showed a recovery of vision almost as good as that in Group IV. This leads to a consideration of the influence on the ERG of traumatic opacities of the ocular media. Cataracts are known to have little effect (Jayle and others, 1968, Tassy, 1966; Tassy and others, 1968; Burian and Burns, 1966), but intraocular haemorrhages may cause more modification. To investigate this we tested normal subjects by inserting glass containers full of human blood between the flash and the subject. The subjects were tested successively with blood thicknesses ranging from 0·5 to 10 mm. We used flashes of intensity 4.

With white stimuli, and up to 1 mm. thickness of blood, the amplitude of the ERG diminishes by only 10 per cent., but the responses get a scotopic pattern; with a 2 mm. thickness of blood the amplitude diminishes to 30 per cent. of the normal; with 3 mm. to 20 per cent., and 5 mm. to zero.

With red stimuli the first millimetre of blood changes neither the amplitude nor the shape of the responses; 2 mm. reduces the amplitude to 50 per cent. of the normal, and with 5 mm. the ERG disappears.

Responses to blue stimuli are much more sensitive; they are reduced to 25 per cent. of the normal by a 0·5 mm. thickness of blood and with 1 mm. the ERG disappears.

The drastic changes obtained experimentally with a 2 mm. thickness of blood (and with only 0·5 mm. for the blue stimuli) seem to contradict our clinical results: normal and subnormal ERGs were obtained in many patients with extensive haemorrhages (*e.g.* Case 3); moreover all patients with extinguished or greatly diminished ERGs, in whom the fundus became visible later, had retinal damage explaining the reduction of the ERG. However several facts may explain the small effect of the blood filter on clinical findings:

(*i*) The blood in the eye is mixed with aqueous humour and vitreous, so that the thickness of the blood filter seems to be greater than in fact it is.

(*ii*) The anterior chamber is 3 mm. deep only in its central part.

(*iii*) Some light passes through the conjunctiva, sclera, and pigment epithelium.

Several reasons led us to think that the amplitude of the responses to white stimuli would be the best criterion by which to classify the ERGs:

(*i*) Our experiments showed that the responses to blue stimuli were too sensitive to the filtration of light by blood to be a good criterion; the b_2/b_1 ratio of responses to white stimuli was similar.

(*ii*) With the stimuli used, the responses to white flashes have a greater amplitude than those to red or blue stimuli, and are therefore easier to measure accurately against background noise caused by the movements of the patient. However, we tried to classify the ERGs by other criteria such as amplitude of the responses to red or blue stimuli, b_1/b_2 ratio, b/a ratio, or amplitude of the oscillatory potential, but none gave a prognosis as accurate as the prognosis given by the amplitude of the responses to white stimuli. Even so the ERG may be modified by opacities of the ocular media and the recording techniques which must be used in these damaged eyes. Therefore, only gross abnormalities of the ERG must be taken into account. This probably explains why patients with subnormal ERGs (Group III) had a visual recovery similar to that of those with normal ERGs (Group IV). Moreover, with the stimuli generally used it would not be possible to diagnose a localized macular lesion, but there was no such case in our series.

Some eyes showed a marked decrease in the amplitude of the responses when the ERG was repeated a few days or weeks after the first. In two cases the fundus became visible later and a retinal detachment was seen. A normal ERG soon after the trauma does not preclude the occurrence of a late retinal detachment which can be diagnosed by a decrease in the amplitude of repeat ERGs.

It has already been reported (Jayle and others, 1965; Karpe, 1945; Henkes, 1957; Straub, 1961; Gliem, 1965) that, in contusions of the eye, the modification of the ERG is approximately proportional to the extent of the retinal damage, but the use of the ERG in serious and recent trauma was not discussed. However, in these eyes, in which oedema and haemorrhage often obscure the fundus the ERG has greater clinical value. Our special recording techniques allowed us to record the ERG during the first few days after the trauma, even in very severe cases.

Summary

The electroretinogram was recorded in 61 cases of recent and severe ocular trauma in which opacities of the ocular media prevented the ophthalmoscopic examination of the fundus. In perforating wounds the usual contact lens electrode was replaced by a hook-shaped eyelid retractor electrode or a skin electrode. This allowed the ERG to be recorded during the first few days after the trauma. All patients in whom the ERG was extremely small or no ERG could be elicited later failed to recover their sight, and contrariwise almost every patient with a normal or slightly subnormal ERG achieved a good recovery of vision, even after very serious trauma. The ERG recorded soon after severe ocular trauma has therefore an important prognostic value.

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Mercury content of the human lens

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In patients receiving prolonged miotic therapy, using drops containing phenylmercuric nitrate as preservative, the anterior lens capsule develops an appearance which is identical to that of mercurialentis (Abrams, 1963), a condition extremely common amongst those who work in an atmosphere of mercury. Only one analysis for mercury has been carried out hitherto on a lens showing mercurialentis (Atkinson and von Sallmann, 1946) and in this case the presence of mercury was reported without an exact figure for the amount detected.

Some doubt has, therefore, existed whether mercury is really present in the lens in such cases or whether the clinical appearance is due to some change in the capsule of the lens induced by mercury.

The fact that only one lens has been so analysed indicates the paucity of clinical material available and the technical difficulties in performing tests for very small quantities of mercury. Few lenses do in fact come to analysis because most patients with mercurialentis retain perfectly normal vision. Recently an opportunity has arisen to analyse the lens of a patient with the appearance of mercurialentis due to prolonged miotic therapy and the associated exposure to phenylmercuric nitrate; advantage has been taken of the method of activation analysis which is capable of detecting extremely small quantities of mercury.

Method

The method chosen was based on activation, by neutron irradiation, of the samples to induce the reaction Hg^{196} (n, γ) Hg^{197} followed by gamma-spectrometry to measure the 0·08 MeV gamma rays and comparison of their intensity with those from mercury standards of known weight given the same irradiation. In view of the low levels expected and the interference of high levels of sodium and chlorine activities usually found in irradiated biological samples, a simple chemical separation scheme was used rather than non-destructive analysis. This also gave the advantage of eliminating possible geometry errors when dealing with low energy gamma emitters.

The procedure used was to seal the samples after weighing them in silica ampoules, taking care to avoid overheating them and causing possible mercury losses. Standards were prepared using weighed amounts of mercuric nitrate solution made to 100 μg. Hg/ml., also sealed in silica. Samples and standards were irradiated in the BEPO reactor in a flux of 10^{12} neutrons/cm.^{2}/sec. for 24 hrs. After a short decay period the sample ampoules were cooled in liquid nitrogen, and then broken and rapidly transferred to a reflux distillation apparatus, where the samples were charred with sulphuric acid and wet-oxidized with nitric acid in the presence of 20 mg. inactive mercury carrier. Care was taken to prevent mercury losses at all stages, and after oxidation the solution was allowed to cool and then neutralized with sodium carbonate. The mercury was then precipitated by addition of NH_4S_x and the precipitate spun off and washed. The precipitate was then dissolved in H_2S-saturated caustic soda and reprecipitated by boiling with NH_4NO_3 solution. Standards were treated in exactly the same way, and after washing the final precipitates were slurried onto weighed counting trays with alcohol, reweighed to determine the chemical yields, and then counted on a gamma spectrometer using a 3″ × 3″ thallium-activated sodium iodide detector. Counting data

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were collected over a period of several days in order to verify that the gamma peaks obtained decayed with a half-life of 65 hours and thus check radiochemical purity. Results were obtained by comparing peak areas for samples and standards at an arbitrary point on the decay curves obtained.

Results

The mercury content of three human lenses is reported in this paper. These lenses were all cataractous. One showed the appearance of mercurialentis and came from a patient who had been using miotics containing phenylmercuric nitrate 0·004 per cent. for several years for glaucoma. The other two lenses did not have the appearance of mercurialentis, and came from patients with senile cataract only. The lens from the glaucoma patient showed 1·08 parts per million of mercury, and the other two lenses showed 0·08 and 0·03 parts per million respectively.

The lenses were removed by identical techniques by one of us (U.M.) and care was taken to use no local medications containing phenylmercuric nitrate as a preservative. Alpha-chymotrypsin was used and the lens was delivered "head-first" in order to avoid any instrumentation to the central region of the anterior lens capsule.

Comment

The technique used for estimating mercury is probably accurate to within ±5 to 10 per cent. and the limits of determination of mercury by activation analysis are between 10^{-8} and 10^{-10} g., a range which is very much below the quantities reported here. The mercury content of the suspected mercurialentis lens is therefore some twenty times higher than the content of the senile cataractous lens with most mercury in it.

Little is known about trace elements of the human lens, but in other parts of the body 0·05 parts per million of wet weight is about the highest mercury content which has been recorded. The figure of 1·08 parts per million must therefore be considered pathologically high for the lens showing the appearance of mercurialentis. This is particularly so in view of the fact that the mercury content relates to the lens as a whole and if, as now seems reasonable to conclude, the mercury is present in a small area of the anterior capsule, the concentration at that site must be considerably greater.

It is interesting to speculate on the precise cause of the beautiful appearance of mercurialentis on the slit lamp. Assuming that a human lens weighs about 200 mg., the amount of mercury present in the mercurialentis sample would be about 0·2 μg. The exact thickness of a film produced by this amount of mercury in an area of perhaps 3 sq. mm. will depend upon the form in which the mercury is present. As it is known that mercury can be deposited from solutions of phenylmercuric nitrate, the film itself may be composed of metallic mercury absorbed onto the capsule. Should this be so, the thickness of the film works out somewhere in the region of 0·01 μ, some fifty times smaller than the wave length of mid-spectral visible light. It is therefore hardly to be expected that this would present any significant obstruction to the transmission of light from aqueous humour through the lens.

According to Heavens (1968), a world authority on the optical properties of thin films, a layer of mercury of this thickness could be expected to have a slight granularity rather than to appear as a true film, and according to the particle size coloured effects might be obtained from oblique illumination. These features are well known clinically in all the metalloses which affect the lens. It appears to be impossible to identify the chemical nature of the film merely by inspection of its optical properties, because these depend on the characteristics of the particles rather than on the chemical composition.

Summary and conclusions

A cataractous lens was removed from a patient also suffering from chronic glaucoma. Miotic drops containing phenylmercuric nitrate 0·004 per cent. as a preservative had been used three times a day for 4 years and the lens showed the appearance of mercurialentis. It was found to have a significantly higher mercury content than that of two other cataractous lenses. Although it has not been possible to identify the precise site in the lens where this mercury is localized, these analyses suggest that the appearance of mercurialentis is due to the deposition of either metallic mercury or a compound containing this metal.

The authors wish to express their thanks to Prof. Barrie Jones, from whose patients the material analysed in this paper was obtained, and to Dr. D. Gibbons of the United Kingdom Atomic Energy Authority who gave valuable technical advice, carried out the investigations of mercury, and is largely responsible for the account of the methods used for so doing which are included above.

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Experimental study of cartilage setons

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Approximately 10 to 20 per cent. of primary external fistulizing procedures fail to effect long-term reduction in intraocular pressure (Nadel, 1966). Because of this failure rate, the introduction of foreign materials including silk sutures, gold wires, and hairs to maintain patent sclerostomies has been attempted (Rollet and Morean, 1906; Zorab, 1912; Mayon, 1912). A conductive seton was introduced by Stefansson (1925), who used a tube to connect the anterior chamber and subconjunctival space.

Recently, newer plastics and silicone setons have been used in experimental filtration procedures (Bietti, 1955; La Rocca, 1962; Ellis, 1960; Richards and Van Bijsterveld, 1965). Their advantage has been the very slight foreign body reaction, but as with other foreign materials, there is still a tendency for the seton to slip into the anterior chamber or to be extruded from the wound (Ellis, 1960).

The current investigation was designed to produce an experimental seton model in rabbits, using tubes fashioned from autogenous rib cartilage. Since this substance should be well tolerated and integrated into surrounding tissues, the problems of rejection and slippage should be negligible. In addition, the production of successful filtering blebs by this method might provide an experimental tool to explore the histopathology and mechanism of bleb production and failure.

Material and methods

Albino and pigmented rabbits were anaesthetized with intravenous pentobarbitone. Fur was clipped from the chest, the underlying skin was sterilized, and 1·5 cm. lengths of either eighth or ninth rib cartilage were removed through longitudinal paramedian incisions. Cartilagenous tubes 3 to 6 mm. in length with external diameters of 1·5 mm. and lumina of 1 mm. were then fashioned by appropriate drilling.

Broad superior limbus-based conjunctival flaps were then created and the anterior chamber was opened for a diameter of 3 mm. at the limbus. The autogenous cartilage tube was then inserted 1 to 2 mm. into the anterior chamber, the remainder resting in the subconjunctival space. No fixation was used. Before the conjunctival incision was closed with a continuous 6–0 black silk suture, heparin was injected through the tube to reduce aqueous coagulation.

All eyes were examined periodically with the slit lamp, and intraocular pressures were measured by Schiötz tonometry. Gonioscopy was carried out on all eyes before enucleation.

Adequacy of filtration and demonstration of patency of the fistulae were demonstrated in two ways. If a thin polycystic bleb formed, the Seidel test was sufficient to demonstrate filtration. When diffuse blebs were noted, methylene blue was injected into the anterior chamber and the bleb site inspected with the slit lamp for the appearance of the dye. Fig. 1 (opposite) demonstrates a cartilagenous tube *in situ*.

Results

Autogenous cartilage setons were inserted into 57 rabbit eyes which were observed for varying periods up to 6 months. 33 eyes were enucleated for histological study within 2

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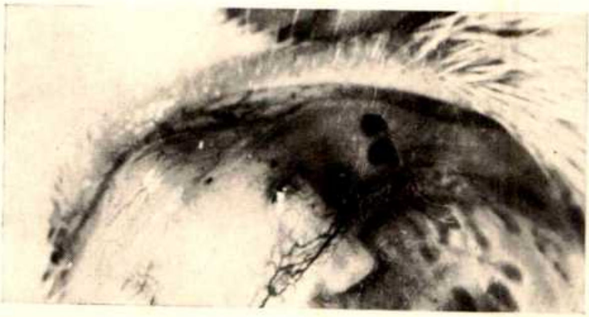


FIG. 1 *Cartilagenous tube* in situ 10 *days after implantation. Note filtering bleb*

months while the blebs were still actively filtering (Table I), and 22 eyes were enucleated within the week after filtration ceased (Table II). Two eyes with well-functioning blebs 6 months after surgery were retained in order to continue clinical observation.

Table I *Time between date of surgery and enucleation of* 33 *eyes with functioning blebs*

Number of eyes	*Days*
11	10–20
11	20–30
11	30–40

Table II *Interval between date of surgery and clinical evidence of bleb failure in* 22 *eyes, which were then enucleated within one week*

Number of eyes	*Days*
3	7
5	15
4	21
4	27
3	35
3	48

In no case did the seton become dislocated into the anterior chamber. No relationship was noted between the length of the implanted tube and the success of filtration.

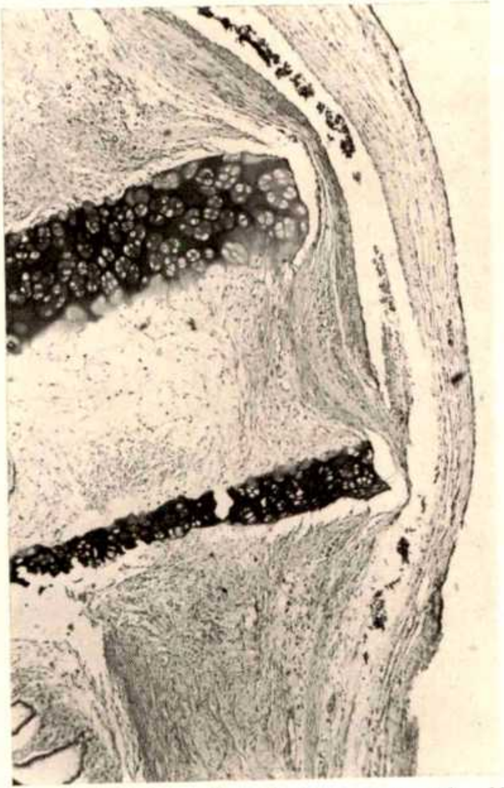
Clinically, most eyes showed mild transient inflammatory reactions about the implant which usually resolved within a week. In only two instances did considerable corneal oedema and vascularization develop at the operative site. In most cases, slight iris atrophy was noted at the site of iris contact with the inner end of the tube. In twelve of the 57 eyes studied, gonioscopy revealed iris tissue in contact with the inner end of the tube, but this did not preclude successful filtration.

Histological examination of eyes in which bleb closure developed revealed the growth of vascularized connective tissue from the episclera into the seton (Fig. 2, overleaf). In no case, however, did proliferation continue into the anterior chamber. The inner surface of most tubes developed a cellular lining resembling endothelium (Fig. 3, overleaf). Although this cellular lining advanced further than the connective tissue, it did not reach the anterior chamber in any case.

Examination of eyes with patent fistulae also revealed an ingrowth of connective tissue with a similar endothelial-like lining, but in these cases, the connective tissue remained peripheral and did not obstruct the lumen.

Discussion

The rationale for autogenous material as an experimental seton was to preclude an immune cause of rejection (Craigmyle, 1955). Cartilage was chosen as the experimental tissue



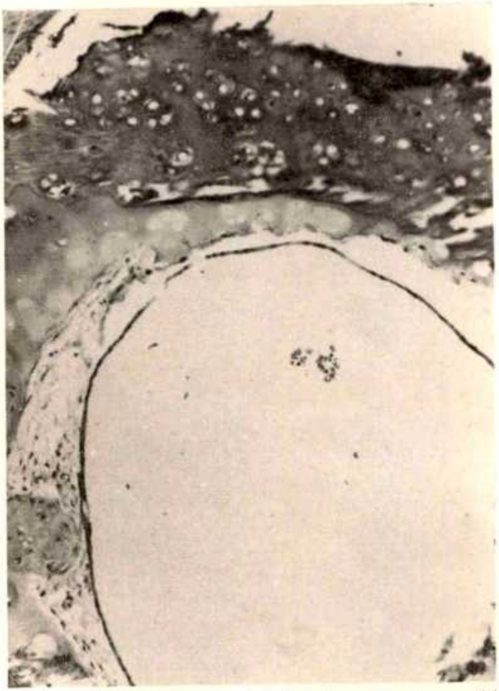


FIG. 3 *Cross-section of tube, demonstrating mild connective tissue proliferation with endothelial-like lining.* × 100

FIG. 2 *Oblique section of tube near outer end. Note early ingrowth of connective tissue.* × 100

because it is readily available, is avascular, does not swell or change its texture, is not too hard, is malleable, and lends itself to working with drills and other tools (Davis and Gibson, 1956; Peer, 1955). Living tissue could also be expected to be incorporated into surrounding tissues, precluding the need for fixation. Yet, in this study, 24 of 26 eyes had failed within 6 months and, presumably, the majority of the remaining 33 eyes would have failed had they not been enucleated while the blebs were operative during the early post-surgical phase. These latter fistulae, though patent at the time of enucleation, permit analysis of the process of bleb closure.

It has been inferred that either endothelium or endothelial-like cells form a protective barrier which prevents aqueous from causing digestion of scleral collagen (Teng, Chi, and Katzin, 1959). It is possible that a sclerostomy lined with such an endothelial covering would preclude the progressive polycystic formation noted after certain types of filtering procedures. In particular, it has been observed clinically that the iridencleisis operation does not usually result in a polycystic bleb. This may be due to the epithelial or endothelial covering of the tract provided by the iris, even though it is presumed that iris endothelium is more permeable to aqueous than corneal endothelium. There is little evidence to support the view that aqueous stimulates a fibrotic response of the subconjunctival tissues (Epstein, 1959). The aqueous pathway, after an iridencleisis, would be similar to the conductive mechanism provided by a physiological seton as in this study.

Iridencleisis procedures, then, are physiological seton procedures. They provide an endothelial-like conductive covering, about a non-conductive seton, the iris. Atrophy of the iris substance occurs and a lined sclerostomy results (Spaeth, 1932).

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2. *Brit. J. Ophthal.* (1956), **40,** 159
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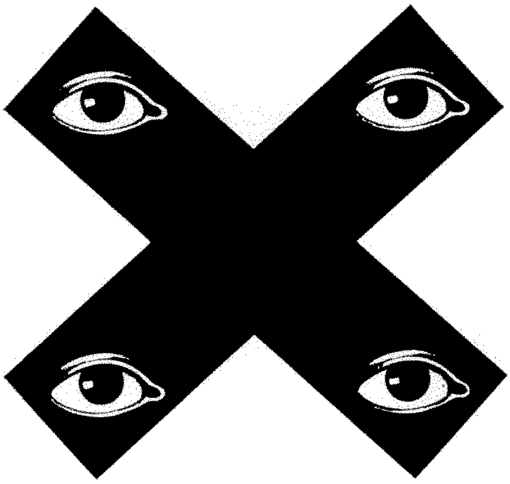

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Autogenous cartilage follows a similar route in certain details. The tube becomes lined with endothelial-like cells, probably derived from episcleral tissue. The cartilagenous walls become surrounded by connective tissue but are always identifiable. The main difference, of course, is that the tube is continually conductive while the iris eventually is not. This latter difference may explain the reason for eventual seton failure. Aqueous leaking about an iris wick has an opportunity to initiate scleral collagen digestion. The conductive seton, however, limits scleral aqueous contact and does not lay the groundwork for what appears to be the common denominator of fistula success—an adequate opening bathed in aqueous.

The cause of fistula failure is considered to be due primarily to proliferation of episcleral connective tissue. If this connective tissue becomes lined and thereby protected from the effect of aqueous, the chances of failure are high. With destructive sclerostomies (burning, excision, etc.), little to no endothelial covering of the sclerostomy site results. Instead, a spongy type of tissue frequently fills the gap, behind which a layer of granular sludge is present. These tissues provide little resistance to aqueous passage.

This seton study demonstrates well that episclera will proliferate rapidly and follow close behind an advancing endothelial-like edge. It is interesting that these endothelial-like cells will not continue into the anterior chamber as in the case of epithelial downgrowth.

Most likely, these are endothelial-like cells modified from a pluri-potential anlage while epithelial downgrowth results from a more definitive cell type such as conjunctiva.

It would appear, then, that even with conductive non-immunogenic setons, fistula failure will result if an endothelial-like covering precludes or reduces aqueous contact with surrounding connective tissue and scleral collagen.

Summary

Setons of autogenous rib cartilage were used to connect the anterior chamber and the subconjunctival space to study the mechanism of bleb formation and failure. Connective tissue invades the tube, covered by an endothelial-like lining. This lined conductive system prevents aqueous from reaching the scleral collagen, and polycystic blebs, if formed, do not persist. The histological findings of this study support the concept that polycystic bleb formation requires an adequate sclerostomy continually bathed in aqueous.

The authors wish to thank Dr. I. Michaelson for his assistance in this project.

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Results of partial penetrating keratoplasty related to the size of the graft

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The aim of the present study is to discover the best size for grafts (as judged by the incidence of postoperative complications) for use in partial penetrating keratoplasty for central deep non-adherent corneal opacities measuring 4 to 5 mm. across. Grafts smaller than 4 mm. rarely remain transparent and those above 7 mm. often become opaque and may be complicated by glaucoma (Stallard, 1965). In grafts of 4 mm. or less it is difficult to handle the direct sutures and to allow for peripheral opacification where the graft joins its bed. The resulting opacity may extend to the centre and obstruct the pupil.

The incidence of postoperative complications, such as loss of anterior chamber, anterior synechia, iris prolapse, secondary glaucoma, and graft opacity, was studied in fifty cases.

Case reports

In the fifty cases studied, deep central non-adherent corneal opacities measuring 4 to 5 mm. across were the result of ulcers with mucopurulent or purulent conjunctivitis.

The general condition of the patients was good. There were no septic foci, and conjunctival cultures were negative. The visual acuity was less than 6/60. The anterior chambers and ocular tensions were normal and there was no corneal vascularization.

In all cases normal saline was injected to reform the anterior chamber at the end of the operation. Atropine ointment 3 per cent. and cortisone ointment were applied during the daily dressing postoperatively.

The sizes of the grafts used are shown in the Table, together with the incidence of postoperative complications.

Table *Incidence of complications after penetrating keratoplasty in fifty cases*

Size of graft (mm.)	*No. of cases*	*No. of border-to-border sutures*	*Complications*				*Clear grafts (3 yrs follow-up)*	
			Loss of anterior chamber for a few days	*Anterior synechia*	*Iris prolapse*	*Secondary glaucoma (3 yrs follow-up)*	*No.*	*Per cent.*
5	10	8	1	1	–	1	7	70
5·5	20	10	2	2	1	2	15	75
6·5	10	12	4	3	1	3	5	50
7·5	10	14	5	3	2	4	5	50

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COMPLICATIONS

Loss of anterior chamber was mostly due to lid spasm or strain, and usually occurred on the third postoperative day and persisted for about 4 days. The incidence was higher in the larger grafts. It was the cause of anterior synechia, iris prolapse, and secondary glaucoma.

Anterior synechia was treated by synechiotomy, iris prolapse by excision of the prolapse and wound suturing, and secondary glaucoma by an iris-inclusion operation.

The smaller grafts were accompanied by fewer postoperative complications, and a greater percentage of successes.

Discussion

The operation of partial penetrating keratoplasty requires not only surgical skill and good instruments but also very fresh sterile donor eyes, healthy recipient eyes (apart from corneal opacity), and good general health in the patient. It is also necessary to be very careful to avoid operative and postoperative complications.

The cause of postoperative anterior synechia and iris prolapse with risk of secondary glaucoma is contact between the iris and the graft edge. To prevent this contact during and after the operation, the following measures are necessary:

(1) The anterior chamber must be kept formed after the operation by:

- (*i*) Hermetically sealing the wound by a sufficient number of properly-placed border-to-border sutures;
- (*ii*) Injection of air or normal saline to reform the anterior chamber at the end of the operation (Rycroft, 1957);
- (*iii*) Avoidance of strain (especially lid spasm) that may evacuate the anterior chamber.

(2) The pupil must be dilated to a size larger than the graft from the time the border-to-border sutures are inserted. This can be achieved by injecting subconjunctival mydricaine during the operation, but it is troublesome for the patient to have such injections daily. Local atropine eye ointment 3 per cent. is usually applied daily with the dressing, and this usually dilates the pupil to about 6 mm. especially in a dark iris with postoperative mild iritis. The graft must therefore be 5 to 5·5 mm. across. Larger grafts of 6·5 or 7·5 mm. carry the risk of anterior synechia or iris prolapse during the insertion of border-to-border sutures or after the operation if the anterior chamber is lost.

One cannot easily judge the exact centre of the trephine hole opposite the centre of the pupil if the latter is dilated from the start, so the operation is begun with the host pupil constricted by pilocarpine. After the site of the circular trephine has been marked, a subconjunctival mydricaine injection is given. When the disc of scarred cornea and the donor disc have been removed, the host pupil is dilated outside the graft edge and the surgeon can begin the border-to-border sutures without any risk of anterior synechia.

The 5 to 5·5 mm. penetrating keratoplasty has the following advantages:

(1) Quicker wound healing with eight to ten border-to-border sutures,

(2) Quicker formation of the anterior chamber,

(3) Less likelihood of loss of anterior chamber,

(4) Easier nourishment of the graft in its early days, and less tendency for graft vascularization and opacification.

As the pupil dilates easily to about 6 mm. with local atropine 3 per cent., these smaller grafts make the development of anterior synechia or iris prolapse less likely.

Summary

(1) Fifty cases of central deep non-adherent corneal opacity 4·5 mm. across were treated with corneal grafts of different sizes from 5 to 7·5 mm. to find out which were followed by the fewest complications.

(2) To be sure that during or after operation there is no possibility of anterior synechia or iris prolapse, either during the insertion of the border-to-border sutures or because of loss of the anterior chamber, the graft should be smaller than the dilated pupil. As daily local application of atropine ointment 3 per cent. usually dilates the pupil to about 6 mm. the best size for the graft is 5 to 5·5 mm.

(3) The operation begins with a constricted host pupil to enable the trephine to be correctly centred on the cornea. After the trephine marking has been made, a sub-conjunctival mydricaine injection is given to dilate the pupil.

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Rechargeable battery belt

For use with the indirect ophthalmoscope

E. W. G. DAVIES AND W. M. BUCHANAN
Department of Experimental Ophthalmology, Institute of Ophthalmology, University of London

A rechargeable battery is a convenient form of providing power for an indirect ophthalmoscope when conducting a ward round in a retinal unit, and disposes of the need for connexion to a mains supply at each bedside.

Nickel-cadmium cells are widely used in industry and are admirably suited to the supply of power to ophthalmoscopes because of their almost constant voltage during discharge. The light output is thus reasonably constant. Batteries for supplying ophthalmoscopes are usually designed to be carried in the hand or in a capacious pocket, but these are heavy and bulky, and do not leave both hands free for examination of the patient.

BELT

A battery has been designed in the form of a belt which can be carried unobtrusively and when in use leaves the hand free. Five nickel-cadmium cells are carried in pockets attached to the belt and are arranged to give an even distribution of weight.

ILLUMINATION

A three-way switch is also mounted on the belt giving an "off" position and two levels of illumination. The lower level of illumination is achieved by connecting a half-ohm resistor in series with the lamp. To switch one cell out of the circuit would cause unequal discharge of the cells. This lower level of illumination is approximately 15·5 watts at full charge. The higher level of illumination supplies the 18 watt ophthalmoscope bulb.

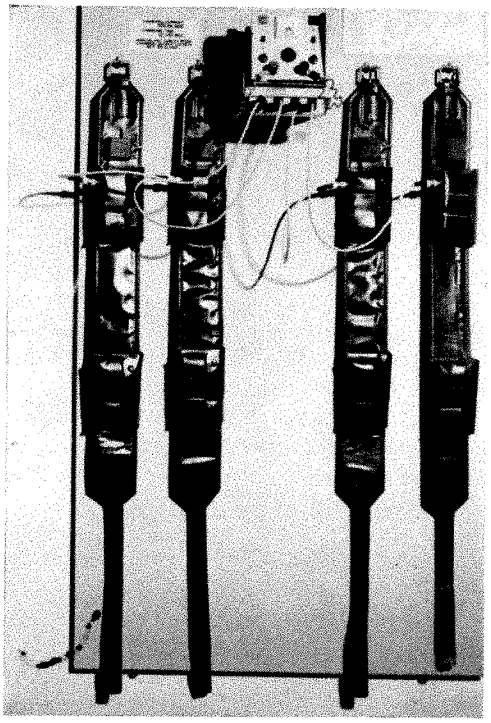

FIGURE *Charger with four battery belts plugged in*

CHARGER

A suitable charging unit, able to charge four belts simultaneously, can be placed in a central position in the retinal unit and belts are connected to this when the ward round has been completed (Figure). The charge is completed in about 12 hours at 350 millampères, and at this rate no damage occurs if the belts are inadvertently left on charge. The cells can be recharged several hundred times and, although their capacity will gradually decrease with time, their life is prolonged if complete discharge is avoided.

The nominal voltage of each nickel cadmium cell is 1·3 volts when fully charged and the five cells in series therefore provide 6·5 volts.

The belt will sustain continuous use of the lamp for up to 2 hours; with the more usual intermittent use during a ward round the duration of supply is considerably longer.

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Book reviews

Fluorescence Photography of the Eye. By EMANUEL S. ROSEN. 1969. Pp. 345, 232 figs. Butterworth, London. (£6 18*s.*)

This volume, primarily by Emanuel Rosen, a senior ophthalmic registrar at the Manchester Royal Eye Hospital, is an excellent production. There is no doubt that since it was first introduced only 9 years ago fluorescence photography of the fundus has developed with unusual rapidity into becoming one of the most useful techniques in the study and diagnosis of retinal diseases, and is consequently of use not only to the ophthalmologist but also to the physician. Our knowledge of the technique and its potentialities in a vast number of retinal diseases, particularly those affecting the macula and the pigmentary epithelium, vascular and inflammatory diseases, and detachments of the choroid and retina, are illustrated in detail with the utmost clarity, and it is interesting to observe how often fundus fluoroscopy at once clarifies the nature of a condition which might give rise to doubt with simple ophthalmoscopic examination. The production of the book is excellent and the photography equally good.

Manual and Colour Atlas of the Ocular Fundus. By HANS-WALTHER LARSEN. 1969. Pp. 312, 523 col. illus. Munksgaard, Copenhagen. (£23 6*s.* 8*d.*)

A review has already appeared in this Journal of *The Atlas of the Fundus of the Eye* by Hans-Walther Larsen of Copenhagen which appeared in 1964; the present volume may be looked upon as a second and enlarged edition of this and is equally excellent. The format has changed for, instead of being a simple atlas, the first part of the volume discusses the descriptions and diagnoses of the various conditions with many references to the figures which constitute its second half. This is copious in coloured photographs of outstanding excellence, and includes not only the common diseases of the fundus but a number of rare conditions seen by the author, all of them accompanied by useful clinical notes on the particular case illustrated. At present we know of no atlas so good and comprehensive and the author and, incidentally, the publishers are to be congratulated.

The Ophthalmologist (Der Augenarzt). 2nd ed., vol. 1. Edited by K. VELHAGEN. 1969. Pp. 849, 355 figs (several col.). Thieme, Leipzig. (DDR 97M.)

It is good to see that the spirit of the enormous Graefe-Saemisch *Handbuch* with its three editions and the shorter *Kurzes Handbuch der Ophthalmologie* is being continued in German literature by the publication of a second edition of the series of volumes which embrace all ophthalmology, edited by Karl Velhagen. The first volume is considerably larger than its predecessor and the contents have been rearranged with a great deal of improvement. The book is the work of several authors; nine well-known authorities have contributed to the subjects of anatomy (Rohen), the physiology of the light-sense (Monjé), physiological chemistry (Pau and Graeber), pharmacology (Velhagen and Graupner), the general management of the ophthalmic patient (Velhagen), methods of examination, including those applicable to the external eye, the anterior chamber and the pupil, the orbit, and the fundus, as well as diaphanoscopy, ophthalmodynamometry, and photography (Heydenreich), the exploration of the visual fields (Schober), the light sense (Comberg and Heydenreich), and colour vision (Heydenreich). In reviewing the first edition of this series in this Journal we said it was good; the second edition is better and very well produced with excellent illustrations. Each subject is treated comprehensively and each section includes a bibliography dealing largely with recent literature. The series ought to be of great value to German readers.

The Practice of Refraction. By STEWART DUKE-ELDER. 8th ed., 1969. Pp. 329, 244 figs. Churchill, London. (45*s*.)

The new edition of this well-established classic has been modernized in several respects and must still remain the work of choice for the tyro in the art of refraction. The section on contact lenses has been brought up to date but it is perhaps inevitable that, in a work of this size, the value of this section as a practical guide is somewhat limited. Nevertheless, this complex subject is presented in all its essentials with the author's unabated literary expertise.

Vision Screening of Pre-School Children. By L. J. TAUBENHAUS and A. A. JACKSON. 1969. Pp. 106, 27 refs. Thomas, Springfield, Ill. ($8.75)

If it is desirable to pursue a policy of seeking out visual disability a climate of public awareness has to be created. This work is intended to demonstrate how such a policy can be applied to the pre-school child. The organization of a screening programme is discussed in simple style as it relates to those carrying it out and to those who will benefit from it and how. The techniques by which it can be realized are also elaborated. The whole turns out to be a combination of elementary paediatric ophthalmology, public relations, and common sense. Being heavily slanted towards the layman the ophthalmologist is likely to learn less of his own subject than of the admirable results of American enthusiasm.

Notes

II Cataract Surgery Congress

Miami, February 6 to 10, 1971

The second biennial Cataract Surgery Congress will be held at Hotel Fontainebleau, Miami Beach, Florida. A preliminary call is made for short papers on any aspect of cataract surgery or related topics. Each paper will be discussed by ten outstanding full-time Faculty Panellists, and also Guest Panellists from a group of surgeons distinguished in their fields. For further information write to Robert C. Welsh, M.D., 608 Huntington Medical Building, Miami, Florida.

Irish Ophthalmological Society

Annual Meeting, April 30 and May 1, 1970

The Irish Ophthalmological Society will hold its Annual Meeting in Dublin on April 30 and May 1, 1970. The Montgomery Lecture will be delivered in the Royal College of Surgeons in Ireland on the afternoon of April 30 by Mr. J. B. Prendiville, F.R.C.S.I.

Brooklyn Eye and Ear Hospital, New York

Symposium on Congenital Eye Disorders, May 2, 1970

A Symposium on the Surgery of Congenital Eye Disorders in Infants and Children, sponsored by the Brooklyn Eye and Ear Hospital, Alumni Association (19th Annual Alumni Clinical Conference), will be held on May 2, 1970, at the Granada Hotel, Brooklyn, New York. For further information apply to: Brooklyn Eye and Ear Hospital, Alumni Association, Att: Mrs. Ruth Pattenden, 29 Greene Avenue, Brooklyn, New York 11238, U.S.A.

II International Orthoptic Congress

Amsterdam, May 11–13, 1971

The International Orthoptic Association will organize the Second International Orthoptic Congress in the International Congress Centre R.A.I. in Amsterdam, The Netherlands, on May 11–13, 1971. The three main themes will be visual acuity, the scope of orthoptics, and squint in disease.

Further information may be obtained from the Congress Bureau, 199 Oudezijds Achterburgwal, Amsterdam-C., The Netherlands.

Obituary

Paul Bailliart, 1877–1969

The ophthalmic world will feel a great blank now that Paul Bailliart has died on October 29, 1969, for he has occupied a unique place in our specialty in the last two generations. He was truly a Frenchman, but in his speeches and in his conduct he was not of France but of the world.

Schooled at Besançon (1884–95) he entered the military medical school at Lyon and acted as an army surgeon from 1902 to 1907 when he went to Paris and initially worked with Morax; thereafter he had a distinguished professional career in that city. His contributions to the whole of ophthalmology were widespread; and he produced three books of great merit: the *Traité d'Ophtalmologie* (1939), with Magitot the *Manuel d'Ophtalmologie* (1950), and *Les Affections de la Rétine* (1933). It was perhaps in the retina that his chief interests lay and his technique of ophthalmodynamometry brought him fame throughout the specialty. He was also interested in history and to his credit wrote two books on this subject.

But it was his wide international relations and his personal qualities that constituted his greatest influence on our specialty. A member of a host of ophthalmological societies he was personally known to most ophthalmologists of his time. The most delightful event in the annual meetings of the French Ophthalmological Society was the lunch at his country house near Paris. You were driven out by an obliging ophthalmologist-chauffeur and after he had found a small space on the verge of the country lane for the car you went into the garden where you were welcomed warmly by your host and his delightful wife and then you met the ophthalmic world as you ate and drank under the trees. If you were asked to this party you had entered the highest ophthalmic circle. Equally respected and loved by all who knew him, he was always genial, kindly, and the soul of courtesy and at the same time completely honest. Fortunately his life was long and full and, with his wife who pre-deceased him, his family and his friends, happy.

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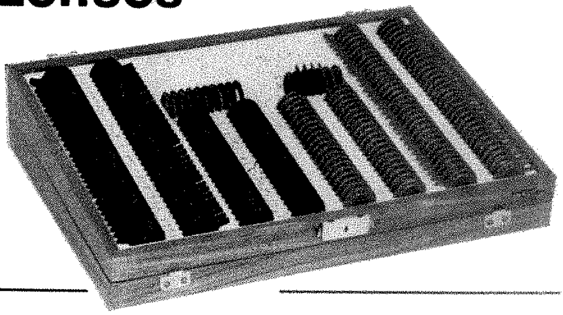

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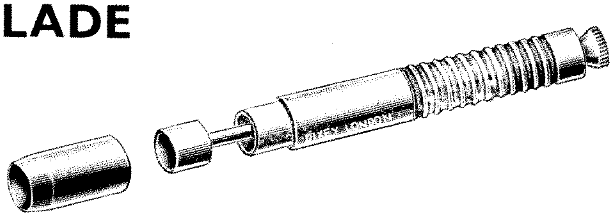

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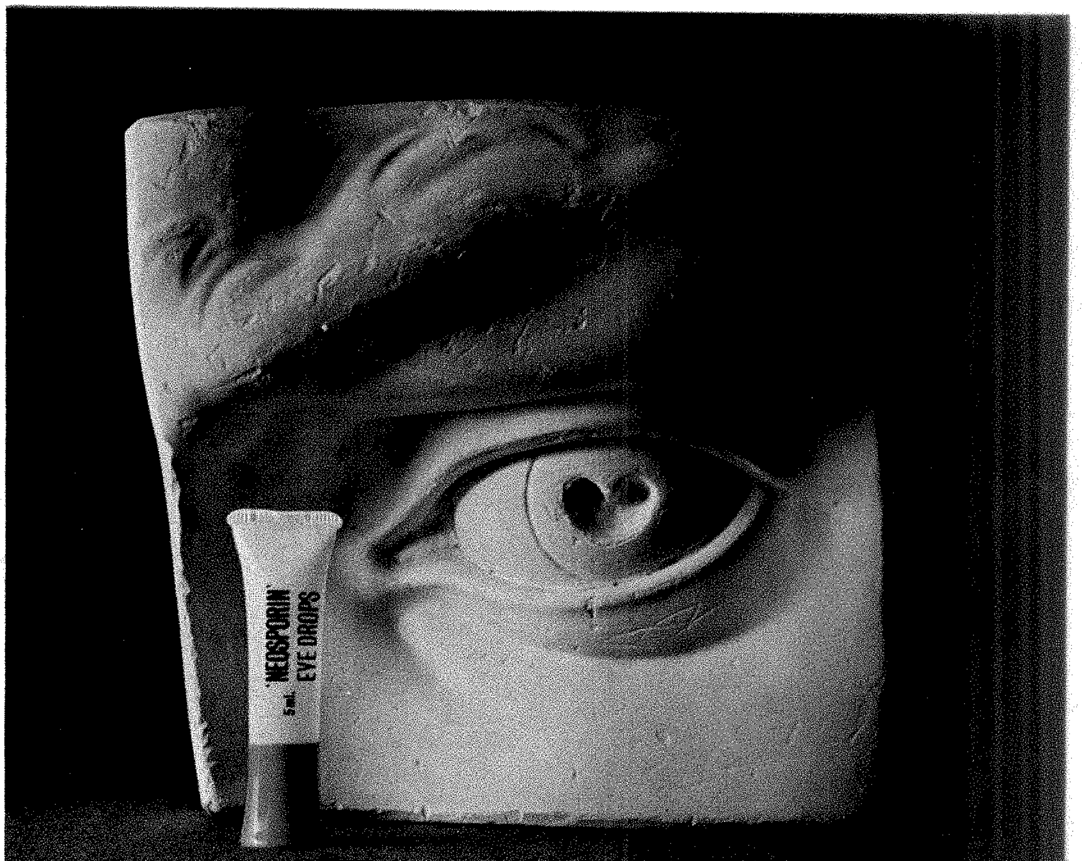

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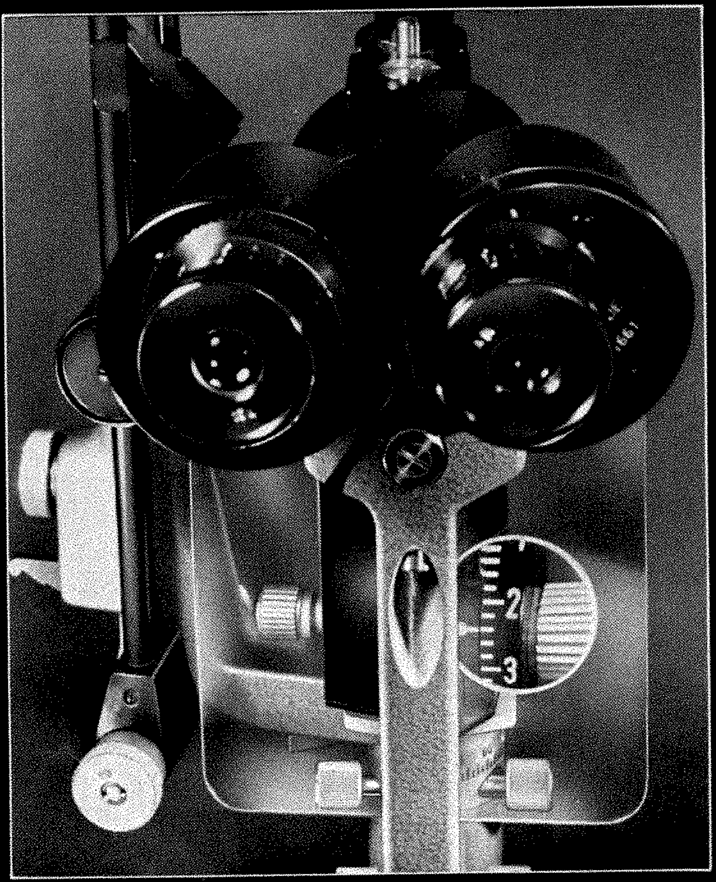

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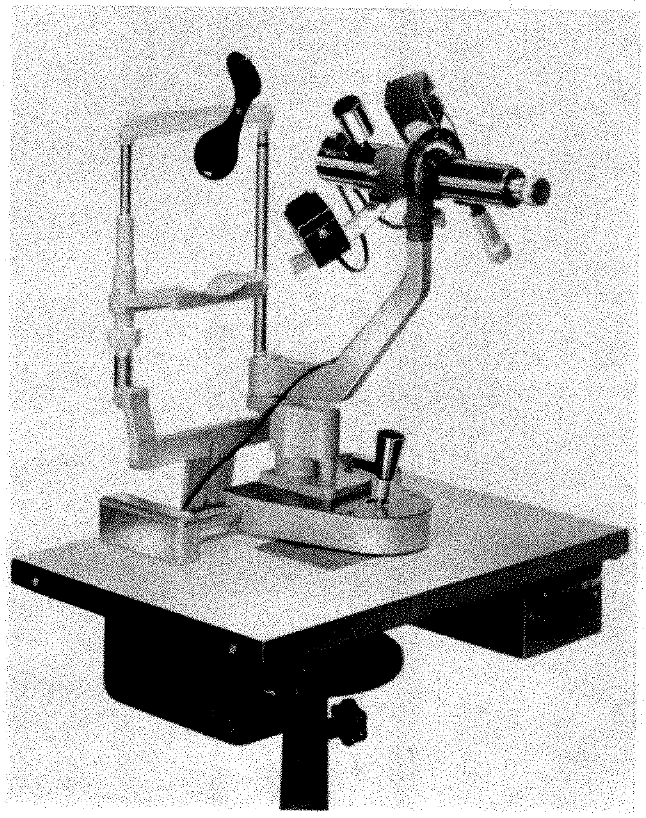

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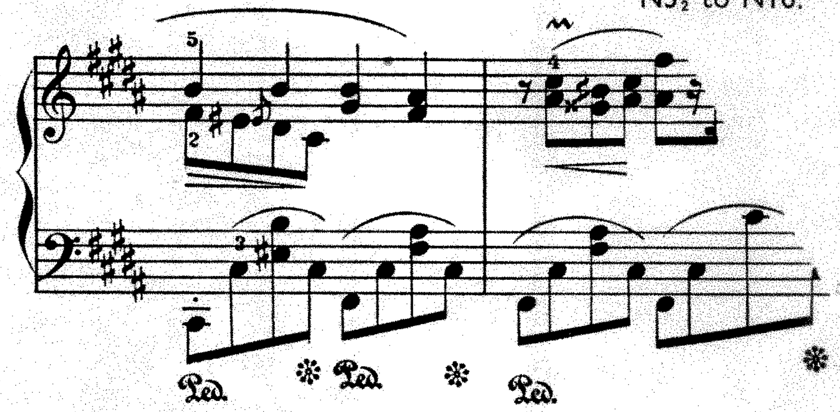

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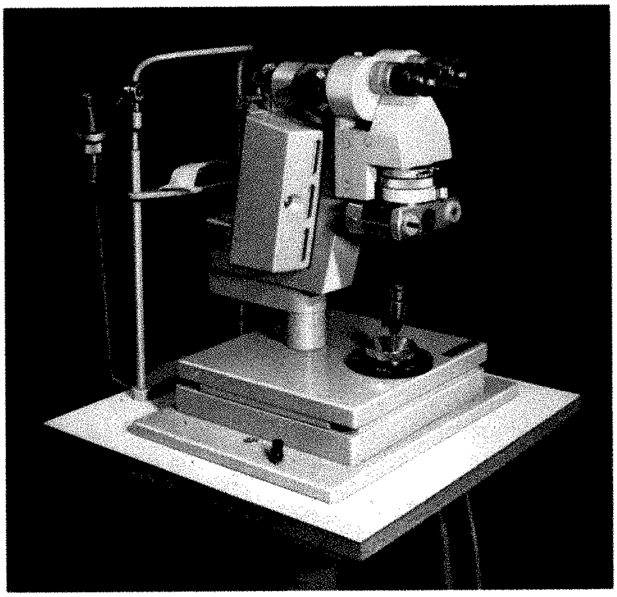

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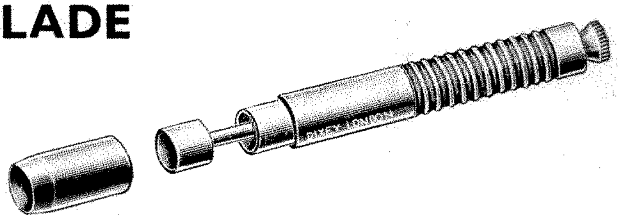

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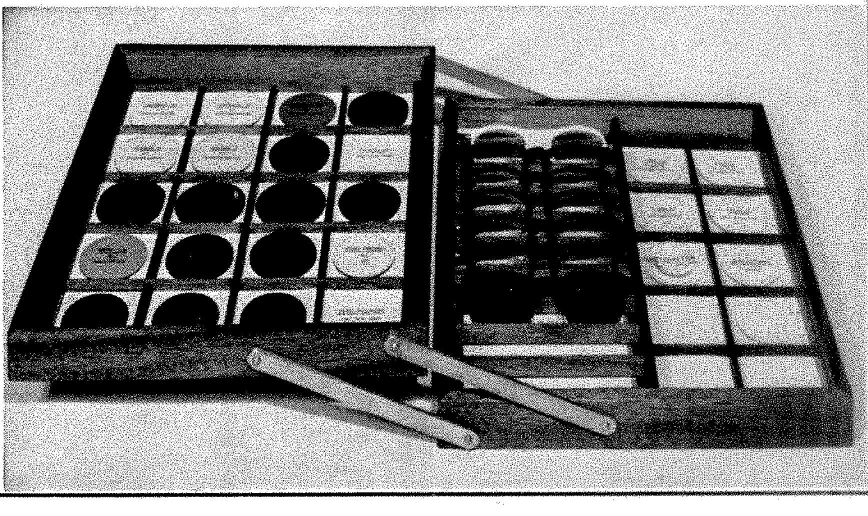

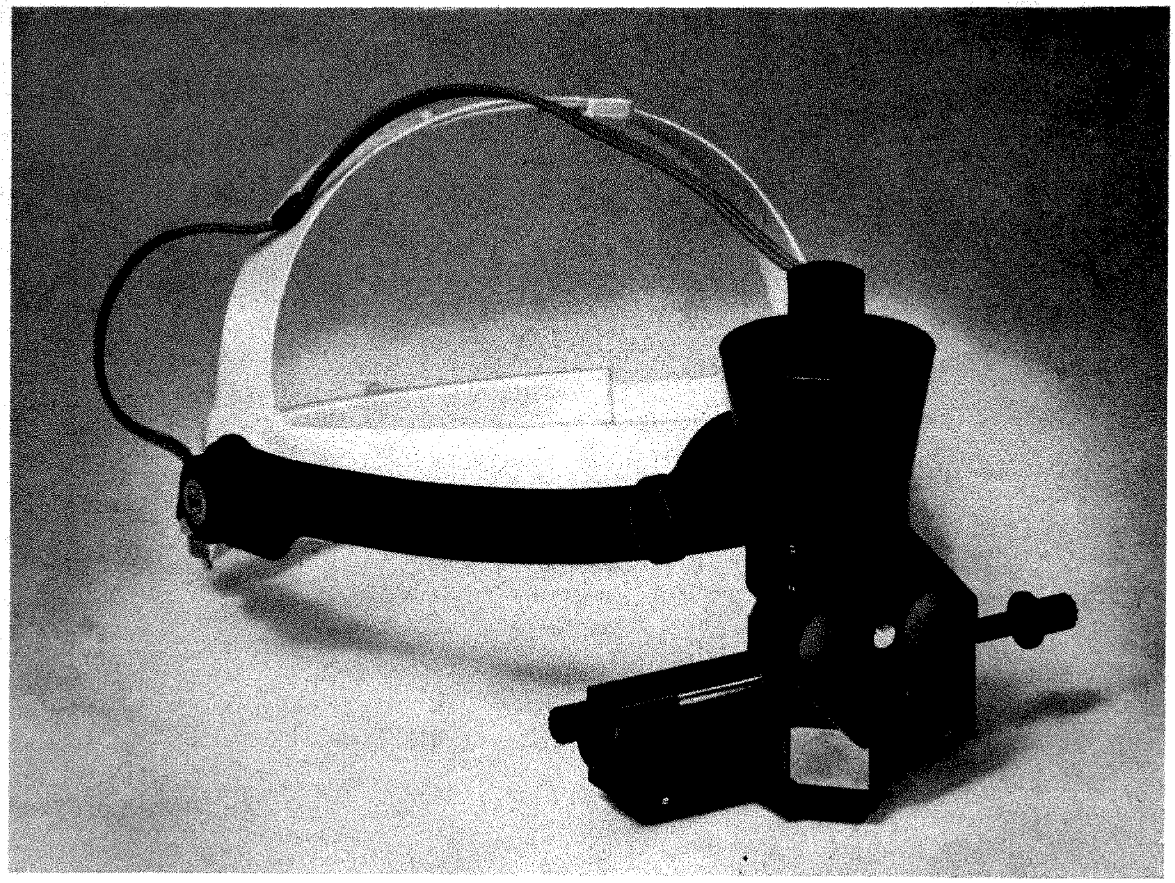

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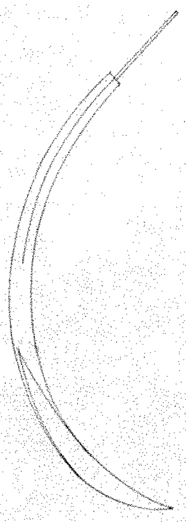

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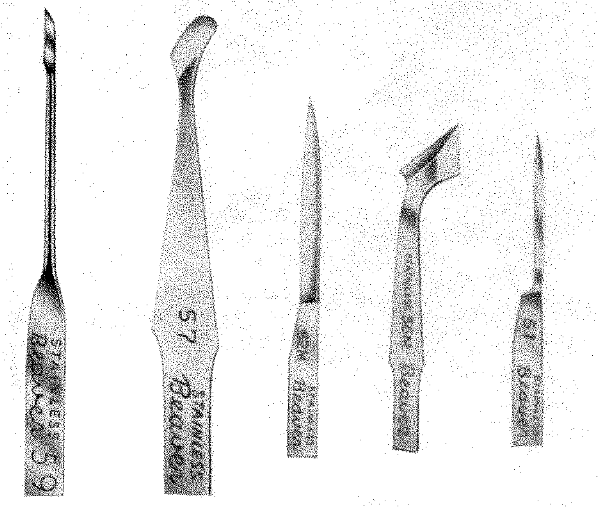

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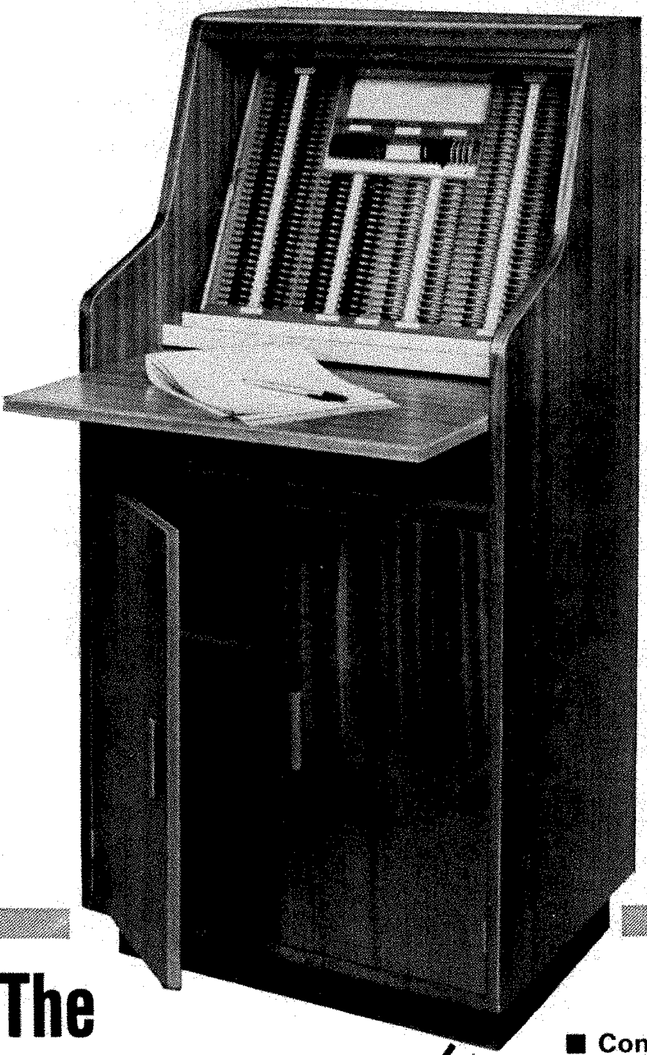

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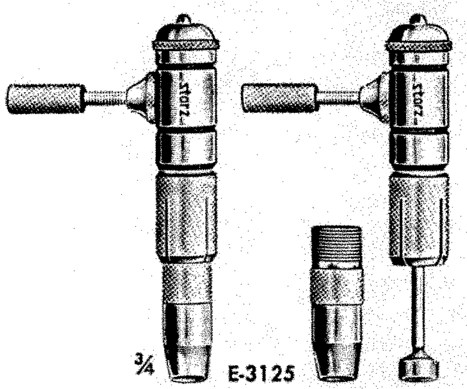

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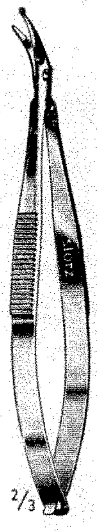

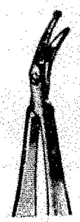

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Communications

Ocular findings in thrombotic thrombocytopenic purpura (Moschcowitz's disease)

S. P. B. PERCIVAL

From the Area Department of Ophthalmology, The Eye, Ear and Throat Hospital, Shrewsbury

Thrombotic thrombocytopenic purpura is a disease of unknown aetiology which affects children or adults of any age but especially young adult females, and which usually proves fatal within a few weeks. The condition was first described by Moschcowitz (1925). Since then various suggestions for terminology have been made, and in Great Britain the more popular names are thrombotic thrombocytopenic purpura (which is now in nearly universal use in the United States of America), Moschcowitz's disease, and (thrombotic) microangiopathic haemolytic anaemia. As the synonyms are unwieldy yet even so do not describe all the characteristic pathological features, and as one should not advocate the use of initials such as TTP, it has been decided in this paper to continue with the simple eponym of Moschcowitz's disease.

The disease is characterized by

(*i*) Widespread plugging of small arterioles and capillaries with fibrinous material,

(*ii*) Fluctuating neurological signs which may vary from transient pareses to deep coma,

(*iii*) Acute haemolytic anaemia,

(*iv*) Thrombocytopenic purpura. It is often also accompanied by fever and renal failure. Should diagnosis be achieved early enough, the treatment (paradoxically) is with heparin (Dacie, 1967; Allanby, Huntsman, and Sacker, 1966; Brain, Baker, McBride, Rubenberg, and Dacie, 1968). Death usually ensues from cerebral haemorrhage, renal failure, or pulmonary oedema.

As visual disturbances are common in Moschcowitz's disease, it is pertinent that ophthalmologists should be aware of their nature, especially as the key to treatment is early diagnosis. This depends to a great extent on the characteristic group of clinical findings since tissue biopsy is often negative. This paper provides the first ophthalmic pathological report on the disease and also a review of the ocular manifestations.

Case report

A housewife aged 19 had been delivered of her first-born child on August 26, 1968. The pregnancy had been without complication. She later suffered from progressive tiredness and on October 17 was re-admitted to hospital.

Received for publication August 25, 1969
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Examination

She appeared pale, slightly jaundiced, and with hepatomegaly and a purpuric rash over her arms, neck, and legs.

Laboratory investigations

Hb 5·9 g./100 ml. falling later to 4·4 g./100 ml.; leucocytes 11,000; ESR 32 mm./1 hr; blood film showed numerous spherocytes and reduced platelets; serum bilirubin 1·7 mg./100 ml. (direct van den Bergh 0·4 mg./100 ml.).

Sternal puncture revealed an extremely active pleomorphic normal marrow. Serum electrolytes, proteins, vitamin B_{12}, folate, SGOT, and alkaline phosphatase, and the prothrombin time were all within normal limits.

Chest *x* ray was normal and abdominal *x* ray confirmed marked hepatic enlargement.

Repeated examination of midstream specimens of urine revealed albuminuria, a deposit showing red blood cells and occasional hyaline casts, and a profuse growth of *E. coli.*

Serological tests for glandular fever, rheumatoid arthritis, lupus erythematosus, leptospirosis, and syphilis were negative. The Coombs test was weakly positive.

Therapy

She was treated with multiple blood transfusions, with antibiotics for the urinary infection, and with prednisolone beginning at 60 mg. daily. She was discharged on November 12, 1968, with the diagnosis of acquired haemolytic anaemia with progressive thrombocytopenia.

Progress

On November 18 she was readmitted with further purpuric haemorrhages, abdominal pain, and vomiting. The pulse was 120/min., BP 130/80. Further investigations revealed Hb 5·2 g./100 ml.; leucocytes 15,000; platelets 50,000; erythrocyte sedimentation rate 25 mm./1 hr; blood urea 85 mg./100 ml. After further transfusions the blood pressure rose transiently to 210/100. She remained afebrile. On November 24 the BP rose transiently to 210/120, and haematuria and melaena developed.

Termination

The patient was restless and complained of visual blurring; 2 days later she developed a left hemiplegia and became deeply comatose until her death on November 28, 1968, only 3 months after the birth of her child.

Ophthalmic examination on November 26, 1968

The visual acuity was unobtainable owing to the patient's drowsy state; the ocular movements were wandering and involuntary; the lids were oedematous; the pupillary reactions were normal and the media clear. The fundi (on mydriasis) were of good colour; the discs and posterior poles appeared normal and there was no evidence of anaemic or thrombocytopenic retinopathy; bilateral retinal detachment was present with ballooning forward of the retina in the left infero-nasal quadrant and the right infero-temporal quadrant; the retinal vessels appeared normal and there was no evidence of a retinal hole, tear, or dialysis. The patient was lying with her head turned to the right.

Post mortem *examination*

Traces of subarachnoid haemorrhage were present over the surfaces of the right cerebral hemisphere; scattered small haemorrhages were present in the white matter of the brain, especially in the left basal ganglia, pons, and the left occipital pole. There was a pericardial effusion; both lungs were moderately oedematous, and haemorrhages were present in the walls and mucosa of the alimentary tract and urinary bladder. The spleen was congested, and infarcted at one point. The cerebral, coronary, and other large arteries were healthy.

Microscopically, the capillaries, venules, and arterioles especially of the adrenal, myocardium, pancreas, liver, and kidney showed a striking occlusive slightly granular fibrinous material, but without inflammatory changes in the vessel walls.

The post mortem diagnosis was thrombotic thrombocytopenic purpura with terminal cerebral haemorrhages.

Ocular pathology

Microscopic section of the eye showed the corneal epithelium to be loose, but Bowman's layer, the stroma, Descemet's membrane, and the filtration angle were within normal limits. There was a mild chronic inflammation in the iris, and the ciliary processes showed some sclerosis. The retina had undergone a shallow detachment (Fig. 1).

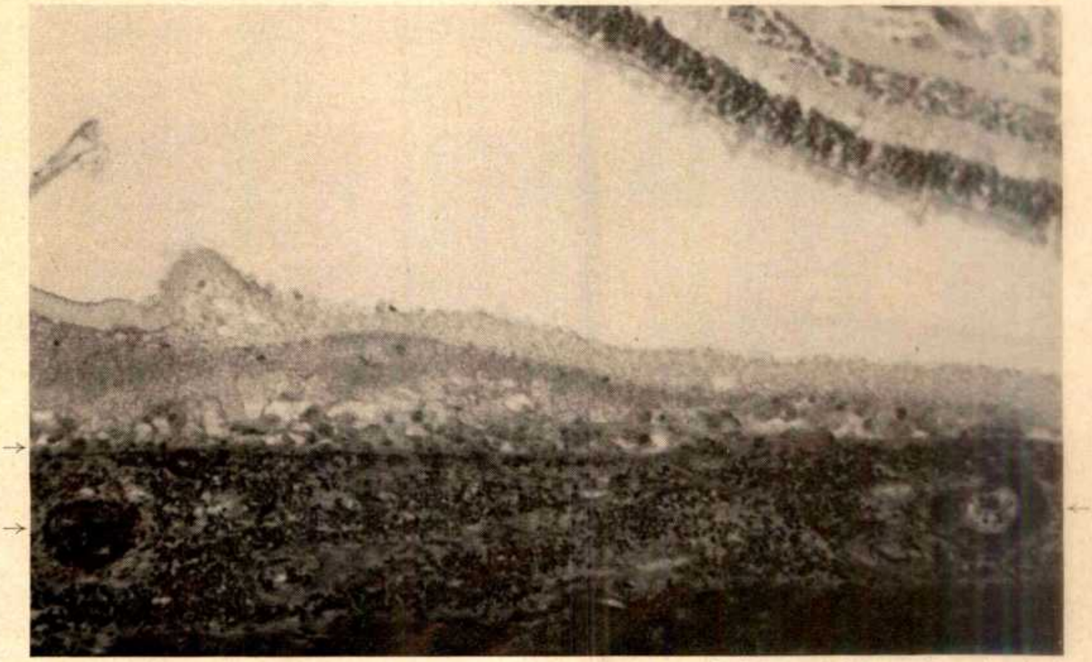

FIG. 1 *Choroid, showing haemorrhagic effusions, vessels containing occlusive material (arrows), and retinal detachment. Mallory's phosphotungstic acid haematoxylin.* × 150

The posterior choroid showed haemorrhagic effusions and some choroidal arteries had thickened walls. Posteriorly some choroidal vessels were obliterated completely or partially by a material which stained for fibrin (Figs 2 and 3, overleaf). This microangiopathy could not be demonstrated elsewhere in the globe. The retinal vessels and optic nerve appeared normal, and no significant change was found in the lens.

Discussion

The aetiology of the disease is not known: an autoimmune process is a possibility, but no specific immunoglobulins have ever been detected and the Coombs test is usually negative. Currently it is thought that the primary defect lies in the vascular endothelium, and is of

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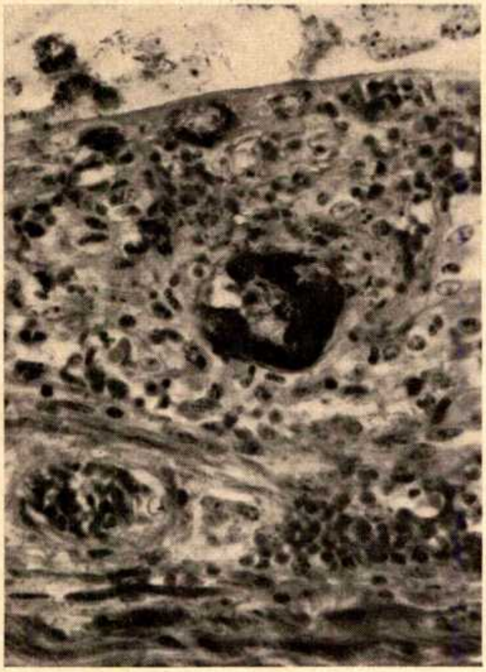

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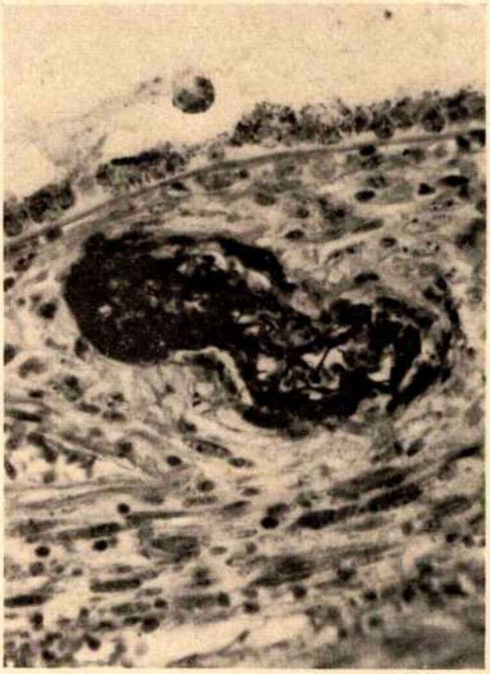

FIG. 2 *High-power magnification, showing occlusive material staining heavily for fibrin in a medium-sized choroidal vessel and also in the choriocapillaris. Mallory's phosphotungstic acid haematoxylin.* × 300

FIG. 3 *High-power magnification of microangiopathy of choroid demonstrating the appearance of intraluminal fibrin strands and the absence of perivascular inflammation. Mallory's phosphotungstic acid haematoxylin.* × 300

allergic origin (Moore and Schoenberg, 1960; Dacie, 1967). Craig and Gitlin (1957), using fluorescein-labelled rabbit antisera against human fibrin, albumin, globulin, and platelets, have shown that the thrombi are composed largely of fibrin and not of agglutinated platelets. Furthermore, recent experimental work (Brain and others, 1968) has shown that deposition of fibrin within small blood vessels may provoke haemolysis and red cell fragmentation. The secondary thrombocytopenia probably results from removal of platelets at the site of vascular damage, and their metamorphosis would be enhanced by the release of ADP and thromboplastins from the fragmenting red cells.

Pathologically, eosinophilic hyaline or slightly granular thrombi are to be found commonly in the small arterioles and capillaries of kidney, brain, myocardium, adrenals, liver, spleen, pancreas, and lymph nodes (Moschcowitz, 1925; Casale, 1965; Amorosi and Ultmann, 1966). There is an absence of perivascular infiltration by inflammatory cells, but adjacent haemorrhages are common. The latter were seen in 80 per cent. of 39 *post mortem* examinations of the myocardium performed by Baroldi and Manion (1967), and are considered to be related to vascular damage rather than to thrombocytopenia (Singer, 1954). Often the occlusion of vessels is incomplete or transient, and sometimes endothelial proliferation may cover the thrombus, producing a crescent-shaped lumen (Symmers, 1952).

In the case under discussion characteristic microangiopathic lesions staining heavily for fibrin were found in the choroid (Figs 1, 2, and 3), liver, kidney, myocardium, adrenal, and pancreas, though sections of the brain revealed only multiple haemorrhages. In

Fig. 3 the appearance of fibrinous strands is well marked and it may also be noted that there is no perivascular infiltration by inflammatory cells.

The clinical ocular findings may be directly related to specific thrombotic lesions or may be symptomatic of the systemic disturbance. In the former group the following may occur:

RETINAL DETACHMENT The detachment in the case recorded (Fig. 1) was undoubtedly exudative in origin, and was most probably directly related to choroidal pathology as when exudative detachment complicates pre-eclamptic toxaemia (Gitter, Houser, Sarin, and Justice, 1968) or polyarteritis nodosa (Sampson, 1945). This condition has not previously been recorded in this disease.

CHOROIDAL HAEMORRHAGE This was present microscopically in the eye sectioned adjacent to areas of microangiopathy (Fig. 1).

HOMONYMOUS HEMIANOPIA This is usually caused by lesions at the occipital poles of the hemisphere (O'Brien and Sibley, 1958, Case 9; Amorosi and Ultmann, 1966, Case 14). There was *post mortem* evidence that this may have occurred in the present case but at the time of the visual blurring it was unfortunately not possible to chart the visual fields. A feature of the cerebral microangiopathy is sometimes the absence of infarction so that the focal signs may be transient and transient hemianopias may result. In more severe cases encephalomalacia results, and in others there may be found petechial haemorrhages, usually in relation to areas of microangiopathy. In addition, some pathologists have reported the presence of cerebral oedema *post mortem*.

O'Brien and Sibley (1958) listed the common neurological presentations of the disease as convulsions, aphasia, cortical blindness, and an organic mental syndrome.

DIPLOPIA There may be involvement of any cranial nerve in Moschcowitz's disease, and sometimes the resulting symptoms and signs are transient. Of the seven patients described by Vassar and Spain (1953), there were three who complained of diplopia, another with an absent corneal reflex due to anaesthesia of the left side of the face, and one with right facial weakness.

ANISOCORIA An enlarged pupil on one side was found in three of the eleven patients described by O'Brien and Sibley (1958). Two patients also complained of diplopia, so that a partial palsy of the IIIrd cranial nerve is a possible explanation. Anisocoria could also be caused by progressive cerebral oedema, and there is a good description of Hutchinson's pupil in one of the cases reported by Symmers (1952).

PAPILLOEDEMA Reports in the literature are sometimes not well documented with respect to aetiology. However, papilloedema has been reported in at least one normotensive patient by O'Brien and Sibley (1958); the patient was also suffering from headaches, nausea, and mental confusion.

RETINAL HAEMORRHAGE This was recorded in about 20 per cent. of the 271 patients reviewed by Amorosi and Ultmann (1966); but in the absence of specific microangiopathy the cause in many cases is probably associated with renal failure. However, Moorhead (1966) raised the possibility of retinal microangiopathy in a patient with perivenous retinal haemorrhages and quoted Schaeffer and Collings (1960) as having noticed in their case sludging in the retinal arterioles.

Eye signs that are symptomatic of the accompanying renal failure, thrombocytopenia, or haemolytic anaemia, include retinal haemorrhage (Brain and others, 1967: Case 7), papilloedema (Dunea, Muehrcke, Nakamoto, and Schwartz, 1966: Case 1), hypertensive retinopathy (Dacie, 1967: Case 32, and others), purpura or oedema of the lids, chemosis and subconjunctival haemorrhage (O'Brien and Sibley, 1958: Case 2; Krentz and Ober, 1967), and scleral icterus.

Vegetations on the heart valves occasionally occur. These were recorded in 10 per cent. of the 157 cases reviewed by Casale (1965); an embolus may then be the cause of retinal vascular insufficiency as in the case described by Cahalane and Horn (1959).

Summary

A case of bilateral exudative retinal detachment is recorded for the first time in a patient with Moschcowitz's disease (thrombotic thrombocytopenic purpura). The frequency of visual disturbances in the disease and the importance of early diagnosis are emphasized, and the various ocular complications are reviewed.

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Karyotype studies among children with severe visual handicap

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During 1963–65, a survey was made of the causes of severe visual handicap, in many cases amounting to complete blindness, among 776 children in special schools in England and Wales (Fraser and Friedmann, 1967). In twelve of these children (Cases 1, 4, 5, 6, 7, 8, 14, 18, 19, 20, 21, 22†), it was possible to perform karyotype studies during the survey, and in one (Case 2†) the chromosomes of a member of the family were examined. In nine further instances (Cases 9, 10, 11, 12, 13, 15, 16, 17, 23†), karyotype analyses had been performed elsewhere, and the results were available; in Case 3† results were available concerning two similarly affected cousins.

In all, therefore, karyotyping was performed, either of the children themselves or (in Cases 2 and 3) of members of their families, in 23 of the 776 subjects of the survey. These children were selected mainly because of unusual constellations of abnormalities; such examinations, however, were also made because of unusual patterns of inheritance of the visual defect.

Case reports

In all these cases, normal karyotypes were found. Basic additional data about the 23 cases investigated are presented in the Table and Pedigrees A to C (overleaf). Screening of the urine was performed in all cases for reducing substances, phenylketones and albumin; in addition, the amino acid excretion patterns were examined chromatographically. No abnormal results were obtained.

Case 1 (Pedigree A, IV, 2)

This girl is probably a heterozygote for sex-linked choroideremia. Such heterozygotes normally show minor changes in their fundi, usually without symptoms. Case 1, however, is involved as severely as any affected male, and a discussion of the possible reasons for this unusual occurrence has been published (Fraser and Friedmann, 1968).

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† These numbers refer to the Table

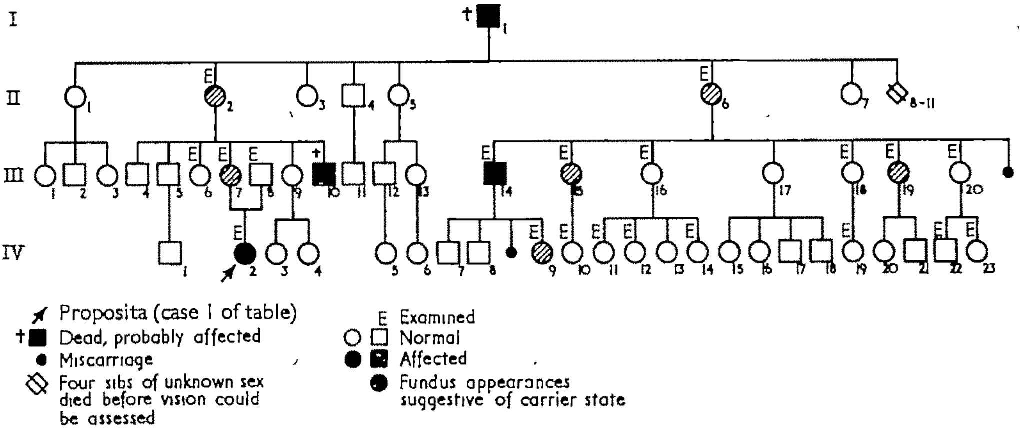
Table *Basic data about children studied*

Case no.	*Case designation**	*Sex*	*Birth rank and total number of liveborn children in sibship*	*Birthweight (lb oz)*	*Parental ages at birth*		*Approximate assessment of intelligence***	*Date of birth*
					Father	*Mother*		
1	A 107	F	1/1	3 4	29	35	N	19.10.43
2	B 39	F	1/2	6 14	22	22	N	28.6.58
3	C 2	M	2/4	5 8	23	21	S	3.12.49
4	F 8	F	1/1	8 7	37	36	A	11.3.49
5	H 2	F	4/6	7 0	28	27	S	23.12.57
6	H 3	F	1/4	7 0	23	19	N	20.2.50
7	H 19	M	2/3	5 13	28	26	S	23.4.48
8	M 3	F	3/3	7 4	34	34	A	9.9.46
9	M 4	M	1/3	6 0	33	31	N	10.4.51
10	M 6	F	2/3	6 12	31	28	S	16.6.54
11	M 8	M	1/1	7 4	27	21	R	18.8.57
12	M 9	M	3/6	6 6	41	31	S	27.7.46
13	M 10	M	1/5	5 0	21	20	S	18.1.51
14	M 15	F	3/3	7 8	33	32	N	13.4.49
15	M 18	M	2/3	7 5	30	29	S	23.6.48
16	M 20	M	1/1	6 3	27	25	S	22.1.53
17	M 25	F	2/2	8 0	26	25	A	15.4.46
18	M 26	F	1/2	6 12	19	22	A	4.8.45
19	M 27	F	5/5	?	?	?	S	4.11.56
20	M 30	F	8/8	6 0	44	43	S	7.4.49
21	M 31	M	2/2	6 12	43	45	R	5.12.58
22	M 33	F	1/2	8 4	24	23	R	18.10.59
23	R 8	M	3/3	6 8	27	?	S	30.1.51

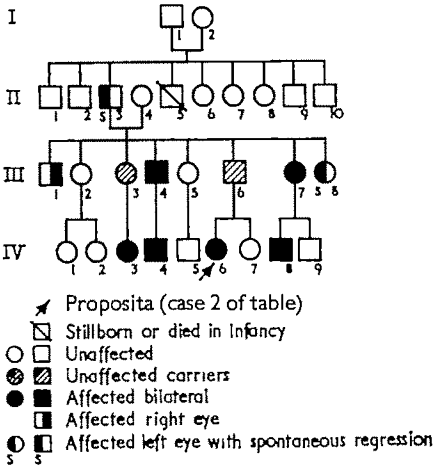
* This refers to the complete report of the survey (Fraser and Friedmann, 1967)

** A Above average S Subnormal
N Normal R Grossly retarded

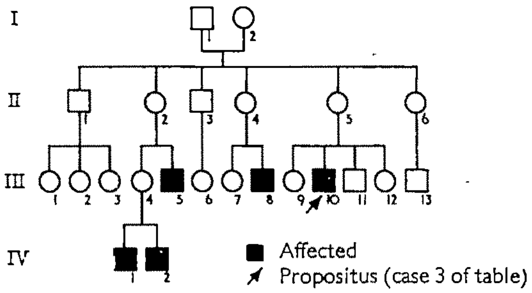
Diagnosis	*Inheritance*
Choroideremia	Sex-linked recessive (pedigree A)
Retinoblastoma	Dominant (pedigree B)
Pseudoglioma	Sex-linked recessive (pedigree C)
Infantile retinal detachment	?Dominant ?Sex-linked
Microphthalmos	?Dominant
Microphthalmos	?Dominant
Anophthalmos; camptodactyly	?
Syndrome of Hallermann-Streiff-François	?Dominant
Rieger's mesodermal dysgenesis of anterior segment	Dominant
Cryptophthalmos; complex malformation	Recessive
Dysplasia spondyloepiphysaria congenita; deafness; myopia; retinal detachments; secondary iritis and cataracts	Dominant
Possibly dysplasia spondyloepiphysaria congenita; deafness; myopia; retinal detachments; secondary iritis and cataracts	?Dominant
Possibly dysplasia spondyloepiphysaria congenita; deafness; retinal detachments; secondary iritis and cataracts	?Dominant
Buphthalmos; megalocornea; hirsutism; skeletal dystrophy	?Recessive
High myopia; cataracts; deafness; skeletal dystrophy	Recessive
Optic atrophy; megalocornea; complex malformation	?
Cataracts; dental deformities; webbed toes; amenorrhoea	?Dominant
Microphthalmos; cataracts; dental deformities; webbed toes	?Dominant
Microphthalmos; lens and corneal opacities; dwarfism; cleft palate; micrognathia	?
High myopia; optic atrophy; polydactyly of hands and feet	?
Extreme microphthalmos; complex malformation	?
Multiple dermoid tumours of eyes and orbits	?
Optic atrophy caused by subdural haematoma; abnormal facies	?


I
II
III
IV
E
Proposita (case 1 of table)
Dead, probably affected
Miscarriage
Four sibs of unknown sex died before vision could be assessed
Examined
Normal
Affected
Fundus appearances suggestive of carrier state

PEDIGREE A *The proposita (IV 2) is Case* 1 *in the Table, a manifesting heterozygote for a sex-linked choroideremia*


I
II
III
IV
Proposita (case 2 of table)
Stillborn or died in Infancy
Unaffected
Unaffected carriers
Affected bilateral
Affected right eye
Affected left eye with spontaneous regression

PEDIGREE B *The proposita (IV 6) is Case* 2 *in the Table and has bilateral retinoblastoma. The chromosomes of her father (III 6), who although normal is clearly carrying the gene responsible for retinoblastoma in this family, were studied*



PEDIGREE C *The propositus (III 10) is Case* 3 *in the Table and has sex-linked pseudoglioma. The chromosomes of his first cousins once removed, IV* 1 *and IV* 2, *were studied*

Case 2 (Pedigree B, IV, 6)

Retinoblastoma is often inherited in a dominant manner, especially the bilateral variety. This family (Pedigree B) shows unusual features, in that both unilateral and bilateral forms occur and spontaneous regression appears to be relatively frequent. Also, at least two persons (III, 2 and 6) who are carrying the responsible gene have no tumour at all. The karyotype of one of these (III, 6—the father of Case 2) was examined and found to be normal; the specimen of skin taken from Case 2, unfortunately, failed to grow.

Case 3 (Pedigree C, III, 10)

This boy is a typical example of sex-linked pseudoglioma. This condition is often associated, as in this family, with mental retardation (Warburg, 1966). Karyotype analysis had been performed on two maternal first cousins once removed of the propositus (C, IV, 1 and 2) and the results were reported as normal by Forrester (1963). One eye of the propositus has been enucleated and histological section showed rosettes, similar to those described in "retinal dysplasia" by Reese and Straatsma (1958), which gave rise to a diagnosis, in all probability erroneous, of retinoblastoma.

Case 4

This girl had congenital retinal folds resulting in total retinal detachments and secondary cataracts at the age of 5 years; the history of her father was similar.

Case 5

This girl had bilateral microphthalmos and has two brothers with bilateral colobomata of the iris, choroid, and retina, as well as a normal brother and two normal sisters. The mother has poor vision, the cause of which is unknown.

Case 6

This girl has bilateral and her sister unilateral microphthalmos with persistent pupillary membrane. Her father has moderate microphthalmos, nystagmus, and poor vision.

Case 7

This boy has bilateral anophthalmos and camptodactyly of both fifth fingers. His mother was treated with thiouracil throughout pregnancy for thyrotoxicosis. There is no family history of visual defects.

Case 8

This girl has the complete syndrome of Hallermann-Streiff as described by François (1958). Her defects include congenital cataracts, microphthalmos, choroido-retinal lesions affecting primarily the macula, hypotrichosis, dwarfism, dental malformations, and a characteristic widespread deformity of the skull with hypoplasia of the facial bones (especially the mandible) and with wide separation of the lambdoid and sagittal sutures. In addition, there was hypertrophy of the occipital condyles and the lateral parts of the atlas. There is no family history of visual defects or of these associated anomalies.

This girl was reported by Gregory (1955), and her photographs, taken from that report, are reproduced by François (1958).

Case 9

This boy has glaucoma associated with partial aniridia in the right eye and complete aniridia in the left. In addition, he has considerable hypoplasia of the maxilla, low-set bat-ears, umbilical hernia, and anal stenosis. His brother is similarly affected except that malformed irides are present in both eyes giving rise to slit pupils. The mother of these two boys also had slit pupils and malformed irides, and the maternal grandmother has suffered from glaucoma for many years, though it is not known whether this has been associated with malformation of the iris.

This family was described by Crawford (1967) as a probable variant of Rieger's mesodermal dysgenesis of the anterior segment (Rieger, 1935). The karyotypes of the mother and both affected boys were normal.

Case 10

This girl suffers from the autosomal recessive syndrome of cryptophthalmos. In her case, this complex and variable syndrome comprises deafness due to middle and outer ear malformations, high palate, webbing of fingers and toes, atresia of the larynx, wide separation of the symphysis pubis, anal stenosis, and masculinization of the external genitalia. A similarly affected sister died a few hours after birth because of renal aplasia which is frequently present in this condition. The parents are normal except that the father has slight microphthalmos, and the mother has a degree of blepharochalasis; these findings may represent mild heterozygote manifestations. This case has been described by Fraser (1962, 1964, 1966).

Case 11

This boy is dwarfed because of widespread skeletal dystrophy. He has congenital cystic detachments of the retina, associated with myopia and resulting in secondary iritis, glaucoma, and cataracts. He (as well as Cases 12 and 13) has been studied independently by Roaf, Longmore, and Forrester (1967), and the *x* rays reproduced in that report leave no doubt that this skeletal dystrophy is of the type of dysplasia spondyloepiphysaria congenita (Spranger and Wiedemann, 1966a, 1966b; Bach, Maroteaux, Schaeffer, Bitan, and Crumière, 1967). This entity is discussed further below. Cleft palate has been reported in cases of this condition; it was present at birth in Case 11 and was subsequently repaired. There is some evidence of moderately severe hearing impairment affecting primarily tones of high frequency. There is no family history of visual defect or of these associated anomalies.

Case 12

This boy is dwarfed because of widespread skeletal dystrophy. Unfortunately, no *x* rays were available for examination, but the clinical history and a single *x* ray of the knee reproduced by Roaf and others (1967) suggest that the condition may be dysplasia spondyloepiphysaria congenita. The patient is blind because of high myopia, leading to retinal detachments, secondary iritis, and cataracts. He has moderately severe deafness of a mixed conductive and perceptive type noted since the age of 7 years. There is no family history of visual defect or of these associated anomalies.

Case 13

This boy has a widespread skeletal dystrophy but is not notably dwarfed, being 51 inches tall at the age of 12 years. He differs in other respects from Case 11 in that he does not have the round face with flattened nasal bridge and slightly protruding eyes which characterizes cases of dysplasia spondyloepiphysaria congenita. Moreover, several series of skeletal *x* rays taken in infancy and early childhood were available for examination and showed a much less significant involvement of the hips and pelvis than is usually seen in dysplasia spondyloepiphysaria congenita. Nevertheless, the visual lesion is strikingly similar to those of Cases 11 and 12 in that the patient was known to have had poor eyesight since infancy and, by the age of 6 years, he already had bilateral long-standing secondary iritis with complicated cataract in the right eye and widespread retinal detachment in the left. At the time of the survey when he was aged 12 years, he had iritis with calcified lenses and superficial peripheral corneal opacities. Moreover, he had mild perceptive hearing loss affecting predominantly tones of high frequency. There is no family history of visual defect or of these related anomalies.

Case 14

This girl has megalocornea and buphthalmos. Operations for the buphthalmos were followed by retinal detachments and secondary cataracts. In addition, she has marked hirsutism with no detectable endocrine basis and an abnormal facies with a flattened nasal bridge. Her fontanelles closed only at 3 years of age; an air encephalogram showed slight to moderate ventricular enlargement. The brow ridges are prominent, and she has a midline ridge on the occipital bone. The upper second molar teeth have five cusps bilaterally. She has spatulate hands. Qualitative screening of the urine for excess of acid mucopolysaccharides was negative. There is no family history of visual defect or of these associated anomalies.

Case 15

This boy has congenital high myopia in both eyes. An operation for cataract in the left eye was performed at 16 months of age. Vitreous haemorrhages and retinal detachments subsequently occurred in both eyes leading to blindness. He has severe perceptive deafness first detected in infancy. A cleft palate was noted at birth as well as profound deformity of skull structure with wide open fontanelles; the parietal and frontal bone formation was so defective when he was born that he was mistakenly diagnosed as an anencephalic. He had club hands and club feet at birth which have improved with orthopaedic treatment. The parents are first cousins. There is no family history of visual defect or of these associated anomalies; a paternal first cousin is said to be suffering from Down's syndrome (mongolism).

Case 16

This boy has infantile optic atrophy and megalocornea. He shows microcephaly and hypertelorism. He is an epileptic and has cerebral palsy of athetoid type. Rectal biopsy showed extensive sudanophilic demyelination of myelin sheaths and marked neuronal satellitosis. There is no family history of visual defect or of these associated anomalies.

Case 17

This girl has congenital cataracts associated with webbed toes and dental deformities. There is no family history of visual defect, but both she and her sister, aged at the time of the survey 24 and 20 years respectively, have primary amenorrhoea.

Case 18

This girl has congenital cataracts with microphthalmos associated with dental deformities and webbed toes. Her mother has been blind in one eye from birth, but the cause of this defect is not known.

Case 19

This girl has microphthalmos, with eccentric pupils, and lenticular and corneal opacities. She is dwarfed (3 ft at 6 years) and has cleft palate and micrognathia. There is no family history of visual defect or of these associated anomalies.

Case 20

This girl has high myopia and optic atrophy associated with polydactyly of hands and feet and obesity. There is no family history of visual defect or of these associated anomalies.

Case 21

This boy has extreme bilateral microphthalmos and an angioma of the lower lid. In addition, he shows lumbar spina bifida occulta, hiatus hernia, hypospadias, deformed auricles, and undescended testicles. The mother had a diagnostic *x* ray examination when she was 7 weeks pregnant. There is no family history of visual defect; a previously stillborn sister was anencephalic.

Case 22

This girl has a dermolipoma of the left orbit, leading to proptosis of the eye and ulceration of the cornea, and also dermoid tumours of the right conjunctiva and optic nerve sheath. She is deaf and epileptic and has an abnormal electroencephalogram. Her mother was a radiographer and was exposed to *x* rays throughout her pregnancy; in addition, she had influenza when 2 months pregnant. There is no family history of visual defects or of related conditions.

Case 23

This boy has optic atrophy and deafness, caused by a subdural haematoma after an accident at the age of 2 years. He has an abnormal face and short limbs. He suffers from gangrene of the tip of the nose, fingers, and toes. There is no family history of visual defect or of these associated anomalies.

Discussion and conclusions

In all 23 families investigated, only normal karyotypes were found on examination of skin and/or blood cells. While serious ocular involvement is extremely common in known syndromes due to chromosomal aberrations (for a comprehensive review, see François, 1967), most of such children are mentally retarded and those showing many of these syndromes, especially those due to D and E trisomy, do not survive infancy. Since the children surveyed here constituted essentially an educable group, it is clear that the mentally retarded blind are grossly under-represented. Nevertheless, some of these children were considered to be only trainable rather than educable and, according to the rough assessment of intelligence (Table), three of the 23 studied were grossly mentally retarded. In addition, no less than nine were educationally subnormal, the remainder being of normal or superior intelligence. As far as possible, these assessments were made independently of the educational handicap associated with the visual defects of the children concerned.

In Case 1, chromosomal examination was undertaken to investigate an apparent anomaly in the pattern of sex-linked recessive or intermediate inheritance normally associated with choroideremia. This girl is exceptional in that only one other apparent heterozygote for sex-linked choroideremia showing severe and early involvement has been described (Harris and Miller, 1968). In view of this, very careful investigations were made of her karyotype from repeated skin biopsies and blood specimens. All these examinations and additional studies of the sex chromatin in buccal smears and skin fibroblast cultures gave no indication of any deviation from a normal female karyotype.

Chromosomal abnormalities have been reported several times in cases of retinoblastoma (Day, Wright, Koons, and Quigley, 1963; Lele, Penrose, and Stallard, 1963; Thompson and Lyons, 1965; van Kempen, 1966; Wilson, Melnyk, and Towner, 1969), and the unusual pattern of inheritance in the family of Case 2 (Pedigree B) was considered to be a sufficient indication for chromosomal study. Similar pedigrees have been reported by Steward, Smith, and Arnold (1956) and by Watillon, Weeks, Mairiaux, and Joachim (1964).

The normal chromosomal findings in Case 3 (Pedigree C) confirm other results in cases of sex-linked pseudoglioma (Warburg, 1966).

Certain features of the retinal detachments in Case 4 and her father were not typical of the usual autosomal dominant variety. Thus, congenital retinal folds were noted in this girl, and, both in her case and that of her father, retinal detachments had occurred by the age of 5 years. Furthermore, myopia was never a feature of her condition nor of that of her father. It was thought possible, therefore, that a sex-linked type of retinal detachment was involved, but this would involve full expression of the condition in a heterozygous female (as in the choroideremia of Case 1), and the normal karyotype renders this explanation unlikely. It seems more probable that this family represents an atypical form of autosomal dominant retinal detachment.

Lele, Dent, and Delhanty (1965) have described colobomatous lesions of the iris associated with a chromosomal abnormality although they concluded that, in their patient, it was doubtful whether the relationship of the two was a causal one. Allderdice, Davis, Miller, Klinger, Warburton, Miller, Allen, Abrams, and McGilvray (1969), however, came to the conclusion that both microphthalmos and colobomatous defects of the iris and retina were fairly frequent components of a syndrome which they defined as being due to a deletion affecting chromosome 13 in the D group. Irregular dominant inheritance is characteristic of the microphthalmos-with-coloboma group of lesions and the chromosomes of two children from this series with this type of lesion and this pattern of inheritance (Cases 5 and 6) were studied. In both cases, normal karyotypes were found.

The syndrome of Hallermann-Streiff-François is probably inherited in a dominant manner (Guyard, Perdriel, and Ceruti, 1962), and Case 8 may represent a freshly arisen mutation. Rieger's (1935) mesodermal dysgenesis of the anterior segment, present in Case 9 and several affected relatives, is certainly inherited in an autosomal dominant manner. Apart from other features often associated with this condition, this boy and his affected brother have anal stenosis; this association with defects of the iris was previously reported by Brailey (1890). While karyotype studies in Case 9 and his affected relatives afforded normal results, it is of considerable interest to note that Schachenmann, Schmid, Fraccaro, Mannini, Tiepolo, Perona, and Sartori (1965) described a somewhat analogous constellation of abnormalities (coloboma of the iris, anal stenosis, and renal malformation) inherited in a dominant manner and associated with a specific chromosomal aberration. It would seem, therefore, that anal stenosis and abnormalities of the iris are associated in two distinct syndromes, one of which may be the result of a detectable chromosomal rearrangement. Dominant abnormalities of this type, in which multiple malformations are associated, may well often reflect a chromosomal rearrangement rather than a point mutation, but this would have to be quite large to be detected microscopically and, in general, there must be a great number of such small aberrations which cannot be observed by present-day methods.

The entity of cryptophthalmos (Case 10) may represent the expression in homozygous form of a gene which causes mild ocular anomalies in heterozygous form (the blepharochalasis of the mother and the microphthalmos of minor degree of the father). This wide-spread malformation syndrome is often lethal since it may include gross renal hypoplasia, and survivors such as Case 10 may be regarded as "Durchbrenner" or "escapers" in the sense of Hadorn (1955), meaning persons who have crossed a threshold of expression of a gene below which non-viability results. Masculinization of the external genitalia is common in females with this condition (Fraser, 1966) and may give rise to ambiguity of sex. In fact, Case 10 was originally thought to be a boy before sex chromatin studies indicated that she had an XX sex-chromosome complement. This was subsequently confirmed by chromosome studies.

Cases 11 to 13 form part of a larger series of children uncovered during this survey (Fraser, Friedmann, Maroteaux, Glen-Bott, and Mittwoch, 1969) who manifest a generalized skeletal dystrophy, in some instances (including Case 11) corresponding exactly to the dysplasia spondyloepiphysaria congenita of Spranger and Wiedemann (1966a, 1966b) and Bach and others (1967), together with high myopia causing blindness due to retinal detachment and secondary cataract, and moderately severe perceptive deafness. Clinical similarities within the entire group, especially regarding the nature of the visual lesion and the hearing loss, suggest that all these cases may represent phenotypic variation within the same basic genetically-determined disease. Such an identity cannot be proved, however, and the possibility cannot be excluded that two or more distinct conditions are represented within this group. Dysplasia spondyloepiphysaria congenita is probably inherited in a dominant manner (Spranger and Wiedemann, 1966a, 1966b) and isolated examples such as Cases 11, 12, and 13 presumably represent freshly arisen mutations.

Cases 14 and 15 represent ill-defined associations of skeletal dysplasias with blindness. The pattern of inheritance is probably autosomal recessive in Case 14, since a girl seen in this survey with a similar condition has a brother who is also affected. The condition of Case 15 is apparently unique and in his case autosomal recessive inheritance is suggested by the consanguinity of his parents.

Cases 17 and 18 are two of a group of three girls among the children surveyed who have congenital or infantile cataracts, associated with dental deformities and other minor malformations. The third of these girls (whose karyotype was not studied) has an ab-

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normality of the carrying angle of the elbows, and, especially in view of the primary amenorrhoea of Case 17, these constellations of abnormalities raised suspicions of the possibility of a chromosomal anomaly affecting the X-chromosomes. In the light of the normal karyotypes of Cases 17 and 18, however, the exact nosological classification of this syndrome must remain in doubt.

In the remaining Cases (7, 16, 19 to 23) unusual combinations of abnormalities occurred in a sporadic manner and the role of genetical factors in their causation is obscure.

While the possibility that the visual handicap of some of the 776 children surveyed is caused by a major structural chromosomal aberration has of course not been excluded, such associations are probably rare. The 23 families selected for study represent a large proportion of the children of the entire survey with unusual patterns of inheritance of visual defect or with bizarre constellations of congenital malformations. No example of any known syndrome connected with chromosomal aberrations was identified in the whole series and, as has been mentioned above, this is not unexpected, since only those children are represented who have survived infancy and are, in the main, educable. A boy with typical Down's syndrome, confirmed by karyotype study as being due to G-autosomal trisomy, was in fact seen at one of these special schools subsequent to the survey. He had been admitted for a trial period at the end of which it was decided that he was not educable. His severe visual defect was due to cataracts, which are often found in association with Down's syndrome.

These negative findings correspond to those of Leydhecker (1964) who studied seven persons with unusual eye malformations selected among the patients of a large ophthalmological clinic. It would seem advisable to repeat surveys of this type to search for relationships between detectable chromosomal abnormalities and eye defects among non-educable mentally retarded persons selected through visual handicap.

Mention must be made, however, of the findings of Chrz, Neuwirth, Karel, and Klouček (1966). In a study which corresponded closely in its methods to the present one, these authors selected ten out of 284 children at schools for the visually handicapped in Prague for karyotype analysis. Of these ten children, two were thought to show an X isochromosome, two to have E trisomy, and two to have G trisomy. These results are all the more remarkable in that the phenotypes of these six children did not correspond to the syndromes normally associated with their karyotypic abnormalities. In the absence of further clarification of these anomalous results, the significance of these findings is difficult to assess.

Summary

Karyotype studies were made in 23 children (or members of their families) with visual handicap sufficiently severe to necessitate special education. They were selected from among the total of 776 studied either because of the presence of complex constellations of malformations in addition to the visual defect or because of unusual patterns of inheritance of the ocular lesion. No abnormal karyotypes were found, despite the high incidence of serious involvement of the eye in defined syndromes due to chromosomal aberrations.

We should like to thank the Principals and other staff of the schools which the subjects of this study attended for facilitating our visits and placing their time freely at our disposal. We are greatly indebted to the Royal National Institute for the Blind for their financial support of this survey of children with severe visual handicaps. We are grateful to Prof. P. E. Polani for his careful review of the manuscript and his many helpful suggestions. Lastly, we would like to thank the children themselves and their families for their unfailing courtesy and patience.

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Blowout fracture of the orbit

Diagnosis and treatment

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One of the earliest descriptions of what is now referred to as blowout fracture of the orbit was reported by Lang (1889). The mechanism involved in this type of fracture was first suggested by Pfeiffer (1943) and later defined and proven by Converse (1962), Converse and Smith (1957, 1959, 1960), and Smith and Converse (1957).

A true blowout fracture of the orbit can occur as a specific syndrome without any other associated facial fractures (the so-called pure blowout fracture) or it can be found in association with multiple facial injuries as is frequently the case in automobile accidents. In general, the ophthalmologist is well equipped to diagnose and treat the pure blowout fracture, but the latter situation usually requires the services of a maxilliary-facial consultant to handle the associated facial injuries. This discussion will deal only with the pure blowout fracture of the orbit.

An examination of the bony orbit quickly reveals two areas of weakness; the orbital plate of the ethmoid bone which overlies the ethmoid sinuses and the orbital floor lying over the maxillary sinus (Fig. 1). A blowout fracture usually occurs when a sudden blow to the eye pushes the intact globe back into the orbit. There is an associated momentary increase in intraorbital pressure resulting in a fracture or blowout through the thin portion of the orbital floor. The posterior displacement and sudden increase in intraorbital pressure can also result in a concomitant fracture of the medial wall of the orbit into the ethmoidal air sinuses. The orbital floor gives way in the manner of a safety valve with herniation of the periocular structures into and through the opening. In this way the globe itself is frequently spared from any serious injury although a small but significant number of patients has been reported in which intraocular pathology has accompanied a true blowout fracture. The mechanism involved in the development of a blowout fracture generally precludes small objects as aetiological factors. That is, a golf ball striking the globe would usually result in a rupture of the globe rather than a blowout fracture, but a larger object, such as a fist, a knee, a dashboard, etc., will result in a blowout fracture. Converse, Smith, Obear, and Wood-Smith (1967), listed the automobile, the human fist, and the human elbow as the most common aetiological factors in a series of 100 cases.

Diagnosis

Early diagnosis and treatment of a blowout fracture is extremely important since the prognosis in such cases is excellent. These fractures should generally be repaired within 5 to 7 days after injury. Late repair of such a condition is frequently difficult because of

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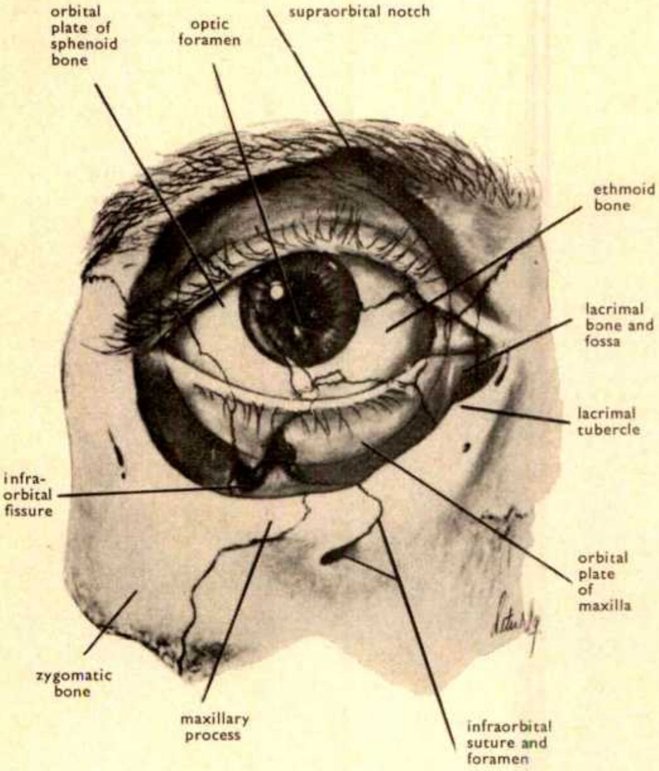

FIG. 1 *Schematic representation of bony orbit and orbital contents*

the associated scar tissue formation and the results are generally not as satisfactory. The most common physical findings observed in patients with pure blowout fractures include (in order of frequency):

(1) Periorbital ecchymosis (Fig. 2)

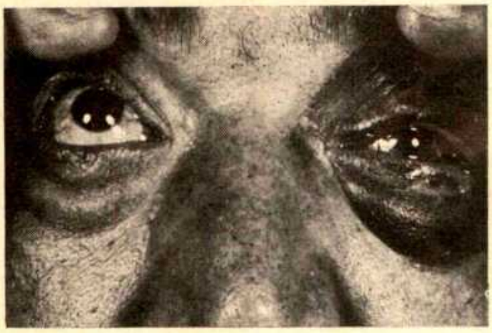

FIG. 2 *Blowout fracture of left orbit, showing oedema, ecchymosis, and inability to elevate the globe*

(2) Inability to elevate the globe (Figs 2 and 3A, overleaf)

(3) Vertical diplopia, hypotropia, or hypertropia on the affected side, depending on the location of the fracture (Figs 4 and 5, overleaf)

(4) Hypoaesthesia over the distribution of the infraorbital nerve

(5) Depression of the globe

(6) Enophthalmos.

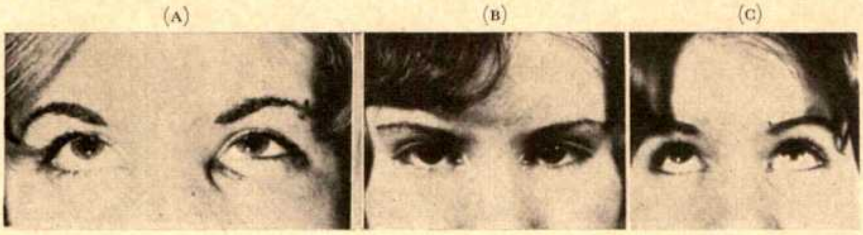

FIG. 3 *Blowout fracture of left orbit, showing inability to elevate globe* (A) *and postoperative result* (B *and* C)

The last is the least common presenting sign, because it is usually masked by the associated oedema and haemorrhage. The frequency with which the other signs are encountered depends on the size and type of fracture. It may develop as a punched-out piece of bone or as a hinged bony fragment of sufficient size to allow a considerable amount of orbital fat as well as Tenon's capsule, the inferior rectus and/or the inferior oblique muscles, to herniate through the torn periorbita. It may also develop as a linear fracture incarcerating some muscle tissue or as a fragment penetrating the inferior rectus muscle.

The typical physical findings usually enable one to make the diagnosis on clinical grounds (Figs 2 and 3A). The initial physical examination may reveal only periorbital ecchymosis, but within 24 to 48 hours the other physical signs generally become manifest. It is therefore important that all patients in whom a blowout fracture is suspected (because of the mechanism of injury) should be followed carefully for several days after the initial injury. This applies even to those patients in whom radiological evidence is also negative. The "entrapment test" (or traction test) may be of value in the doubtful case. In this test local anaesthesia is instilled into the inferior cul de sac and an effort is made to elevate the globe with forceps placed over the inferior rectus muscle.

The extraocular muscle imbalance is due to the entrapment of either the inferior rectus or the inferior oblique muscle or both. It is possible to predict the site of the fracture in relation to the equator of the globe. If the inferior rectus muscle is tethered anteriorly, the eye will be fixed in a depressed position, resulting in a hypotropia on the side of the injury when the opposite eye is in the primary position (Fig. 4). This imbalance will be

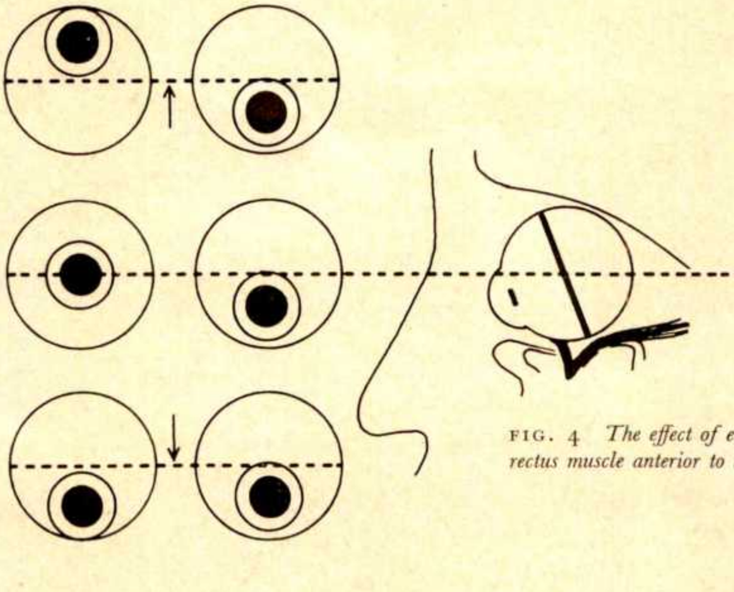

FIG. 4 *The effect of entrapment of the left inferior rectus muscle anterior to the equator of the eye*

less marked on looking down and will be exaggerated on looking up. If the inferior rectus muscle is trapped posterior to the equator of the globe the eye will be fixed in an elevated position and in the primary position of gaze a hypertropia on the same side as the injury will result (Fig. 5). Hence, the imbalance will appear to be less on looking up and will be exaggerated on looking down. If the eyes appear to be straight in the primary position, this usually signifies a fracture located at the equator, and a vertical imbalance can then be demonstrated when the patient looks up or down (Fig. 6). It is, however, important to remember that retrobulbar haemorrhage can result in other nonspecific and variable signs of extraocular muscle imbalance, but these do not usually conform with the above pattern.

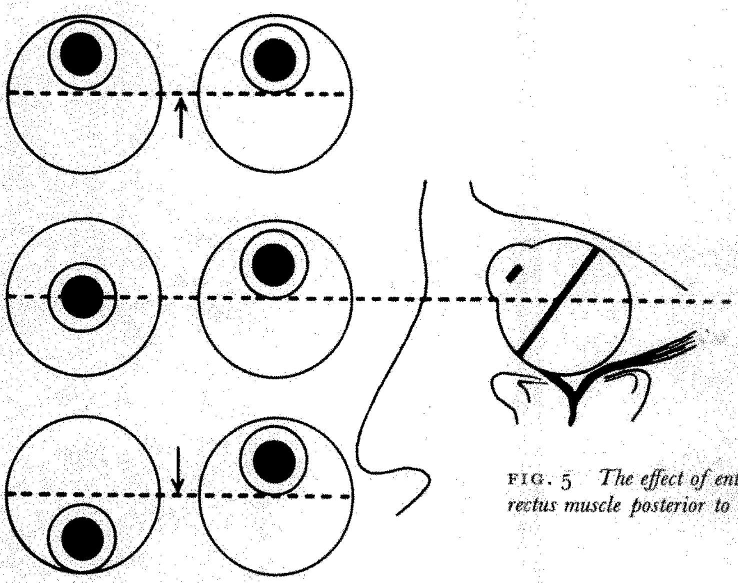

FIG. 5 *The effect of entrapment of the left inferior rectus muscle posterior to the equator*

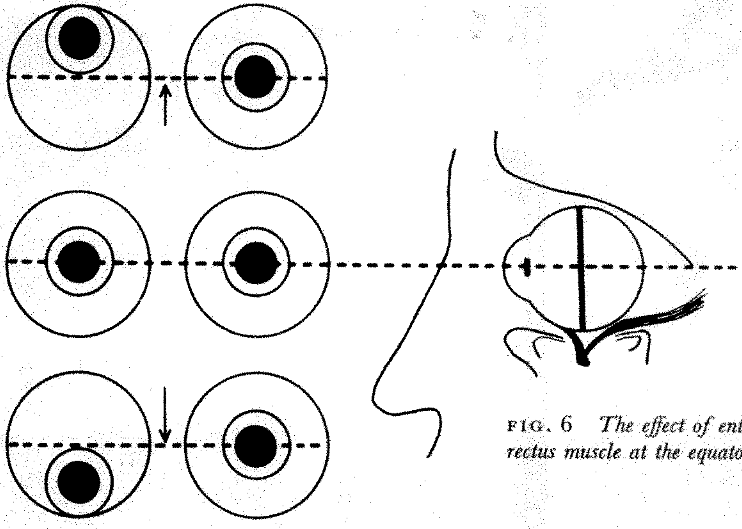

FIG. 6 *The effect of entrapment of the left inferior rectus muscle at the equator*

Between 20 and 35 per cent. of patients may show orbital emphysema which can be due to an associated fracture of the medial orbital wall involving the ethmoid air cells, or the blowout fracture into the maxillary antrum.

Serious ocular involvement associated with blowout fractures of the orbit, while not too frequent (because of the safety valve mechanism involved in the pathogenesis of this fracture), can occur; this may include hyphaema, traumatic iridodialysis, contusion cataract, subluxation of the lens, vitreous haemorrhage, commotio retinae, preretinal haemorrhages, retinal dialysis, and even giant tears in eyes with advanced degenerative retinal changes, and (rarely) traumatic amaurosis with optic atrophy. Secondary glaucoma following subluxation of the lens and angle recession glaucoma have also been reported (Aiello and Myers, 1965; Milauskas and Fueger, 1966). A careful ocular examination is therefore an essential part of the evaluation of any patient with a blowout fracture.

Radiological examination should also be carried out in all patients suspected of having a blowout fracture. These include a slightly modified Waters projection and tomograms (Figs 7 and 8). Stereograms may also prove useful. The radiological findings in a blowout fracture include the following:

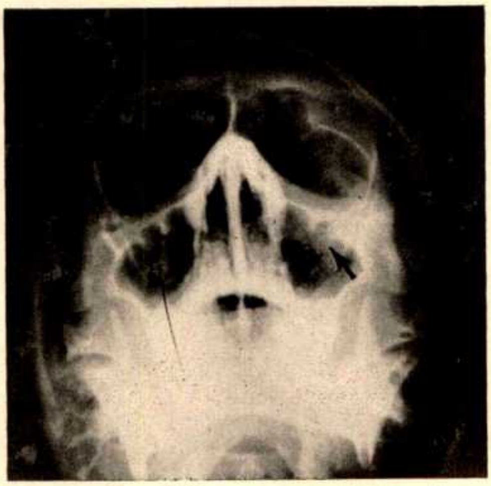

FIG. 7 *Normal Waters x-ray projection. Arrow points to common site of "hanging-drop" opacity in a blowout fracture (see Fig. 9)*

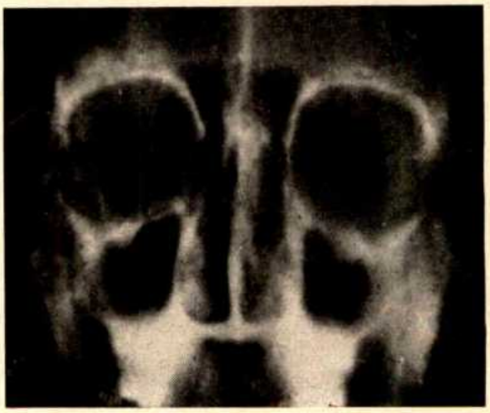

FIG. 8 *Orbital tomogram, showing hanging-drop density in left orbit*

(1) Periorbital oedema, as evidenced by a more radiopaque orbit and thickening of the soft tissue shadow over the inferior orbital rim.

(2) Orbital emphysema, particularly when there is an associated fracture involving the ethmoidal sinuses.

(3) Partial to complete opacification of the maxillary antrum. The opacification is usually due to associated haemorrhage (Fig. 9, opposite).

(4) The so-called hanging-drop opacity into the maxillary antrum (Fig. 9) due to herniation of the orbital contents through the fractured floor.

(5) Fragmentation and irregularity of the orbital floor. In some cases a fragment of bone depressed into the maxillary sinus may appear as a linear density in the soft tissue (hanging-drop) deformity.

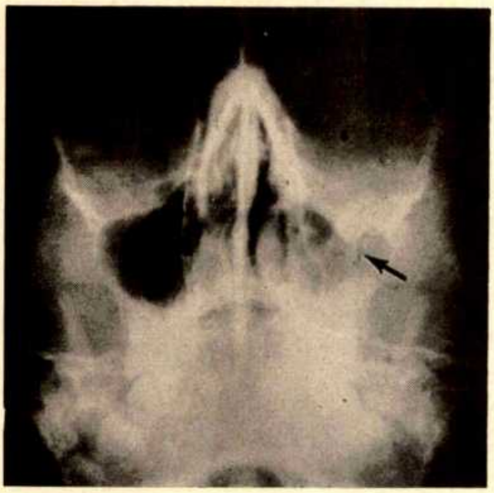

FIG. 9 *Waters projection, showing "hanging-drop" opacity (arrow) in a patient with a blowout fracture of the left orbit*

While radiological examination should be performed in all cases it should be noted that an occasional patient may fail to show any *x*-ray evidence of a blowout fracture of the orbit. In this situation, if clinical signs persist and/or become aggravated over a 24 to 48-hour period of observation, surgical exploration is advisable. In our experience, involving four cases in which radiological evidence (including tomograms) was negative, exploration revealed a significant blowout fracture of the orbit in all of them.

Treatment

The literature of the past 20 years or so is replete with reports of the diagnosis and treatment of blowout fractures of the orbit.* The simplest and most benign surgical approach involves direct exposure of the floor of the orbit and replacement of the blown-out orbital floor with a piece of inert material which is fashioned to fit over the defect at the time of surgery. A variety of materials has been advocated to cover the orbital floor defect, including alloplastics (polyethylene, silicone, Supramid, cranioplast, teflon), tantalum mesh and cable, processed bovine bone, and so forth. Most of these materials appear to be well tolerated and serve as adequate substitutes for the orbital floor. A silicone rubber (silastic) implant less than 1 mm. thick has been used in all our cases. The skin incision is made at the junction of the lower lid with the cheek skin. This incision allows an easy and quick exposure and generally avoids injuring the orbital septum. If the septum is inadvertently penetrated, it is important to repair the defect in order to avoid a baggy eyelid caused by herniation of periorbital fat. The orbicularis oculi muscle is separated in the line of its fibres to expose the orbital rim, and the periosteum is incised and elevated at the upper surface of the rim, enabling a wide sub-periosteal dissection in the orbit. This is necessary in order to demonstrate the herniated tissue. The fat and muscle can then be delivered from the maxillary antrum by gentle manipulation. One should be careful to separate the herniated tissues from the infraorbital nerve. Any loose bony fragments should be removed and a small hook is useful to deliver the bone. A silicone rubber implant (approximately 1 mm. or less in thickness) is shaped to fit over the defect and placed over the floor of the orbit. After it has been checked for proper fit in the sub-periosteal position, it can be left in place without suturing or cementing.

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* See items 1–30, 32–46, and 48–64 in the Bibliography

The blowout fracture is often located some distance behind the anterior rim of the orbit. It is therefore necessary to explore the orbital floor carefully since the fracture might be located in the posterior third. In one of our cases, the fracture was located more than 2 cm. behind the anterior rim of the orbit and extended in a linear direction. Further exploration beyond the initial dissection revealed a fracture site containing a considerable amount of orbital material including muscle tissue.

The postoperative course is very benign and the silicone rubber implants are well tolerated. In over fifty cases of primary blowout fractures treated in this manner (this includes both the pure and impure blowout fracture) with a follow-up of 12 months to 3 years, the postoperative results have been excellent. All of the silicone rubber implants have remained *in situ* without evidence of infection. The elective scars are uniformly pleasing (Fig. 3, B and C) and no pseudoptosis or deepening of the supratarsal sulcus has occurred. Temporary exophthalmos was present in three cases but quickly cleared up. No enophthalmos or exophthalmos is now present in any case. The functional results have also been excellent. In the initial postoperative period a temporary hyperopia may be present but this disappears within 1 or 2 weeks. If the patient complains of diplopia during this time it can easily be treated with a frosted lens or a patch. In the initial postoperative period the maxillary antra frequently remain cloudy, but all postoperative *x* rays have shown clear antra 6 to 8 months after surgery. Several patients had episodes of acute sinusitis but these were easily treated and cleared with medical management.

Discussion

The excellent results obtained with early diagnosis and treatment of blowout fractures of the orbit demonstrate the importance of carefully evaluating every patient who presents with a "black eye". The presence of one or more of the characteristic signs of a blowout fracture should indicate the possibility that such a condition is present. A decision to explore the injury site should be based on clinical grounds which may or may not be supported by radiological evidence (although proper *x* rays including the Waters view and tomograms will demonstrate most blowout fractures). If clinical signs are equivocal, it is best to defer a decision for 24 to 48 hours after which time the patient should be reevaluated. A definite increase in the vertical muscle imbalance warrants exploration. The surgical procedure is simple and benign and the prognosis is excellent.

However, all cases do not warrant exploration. Only those in which the initial or follow-up examination shows positive evidence of blowout fracture with diplopia, enophthalmos, etc., and a positive *x*-ray should be subjected to surgical exploration. Those patients who present with equivocal signs, that is, a minor degree of vertical muscle imbalance only or equivocal *x*-ray evidence or slight enophthalmos, should be followed at daily intervals. If one or more of the clinical signs increases in severity, then exploration as previously outlined seems to be indicated. Some of these cases will remain static for a day or so and then the patients begin to recover from their diplopia without requiring surgical intervention. It is not unreasonable to assume that such individuals might have suffered a small blowout in which there was little or no herniation of the muscles and only a minor degree of herniation of orbital fat.

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Study of the retinal circulation

I. Effect of light

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Our knowledge of the retinal vascular development, structure, and response to various stimuli has increased greatly in recent years. Relatively little is known, however, of the relationship between retinal blood flow and a possible increase in metabolic activity induced by illumination.

We have found only a single published study on the effect of light on the retinal vasculature *in vivo*. By utilizing a scleral window technique, Friedman, Smith, and Kuwabara (1964) studied the retinal circulation under high magnification. They did not detect any change in vessel calibre in response to intraocular illumination by white, infrared, or ultraviolet light. Since the retinal microcirculation can be demonstrated *in vivo* only by means of a microscope with some form of illumination, the effect of retinal illumination may be masked by the viewing light of the microscope.

In this study we have employed a red blood cell staining technique to compare *in vitro* the effects of light-stimulation and dark adaptation on the quantity and distribution of these cells within the retinal vessels.

Material and Methods

GROUP I (CONTROL)

The eyes of eight adult Long-Evans rats (200–250 g.) were removed either immediately after decapitation or under pentobarbital sodium anaesthesia. In four rats one eye had been dilated with Mydriacyl 1 per cent. The enucleations were performed with minimal manipulation, and with the heads maintained in a level position. After several days' fixation in 10 per cent. formalin, the globes were opened, and the retinae were dissected free and stained for haemoglobin by Doherty's modification (Doherty, Suh, and Alexander, 1938) of Pickworth's benzidine-peroxide method (Pickworth, 1934). The retinae were then flat-mounted, either without further processing or after being dehydrated and cleared with alcohol and xylene. Clearing was done on the slide.

GROUP II

Eight rats, in five of which both eyes had been dilated with Mydriacyl 1 per cent. were anaesthetized with ether. A unilateral tarsorrhaphy was performed, and an opaque patch sewn over the closed lids. The animals were then immobilized in a nonconstricting holder, and upon awakening, they were dark-adapted for one hour; the uncovered eye was then exposed for 15 minutes to an ordinary unfocused high-intensity light source at a distance of 2 in. ($4{\cdot}07 \times 10^3$ cd/m.^{2}). The rats were then decapitated and the eyes enucleated and processed as before. The covered eyes were first enucleated in half the rats, and the uncovered eyes in the remainder.

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GROUP III

Six rats were anaesthetized and unilateral tarsorrhaphy and patching were performed as in Group II. After dark adaptation they were exposed to room light ($5 \cdot 04 \times 10^1$ cd/m.^{2}) for 30 min. and then decapitated. The eyes were enucleated and processed as above.

GROUP IV

Five rats, in which both eyes had been dilated with Mydriacyl 1 per cent. were anaesthetized and unilateral tarsorrhaphy and patching were performed as in Group II. After dark adaptation, they were subjected for 30 sec. to a strobe light at a distance of 6 in. ($6 \cdot 8 \times 10^7$ cd/m.^{2}), flickering at the rate of twenty times per second. They were then decapitated and the eyes enucleated and further treated as in Group II.

GROUP V

Seven adult cats (2·5 to 4 kg.) were anaesthetized by parenterally administered pentobarbital sodium and their eyes were dilated with Mydriacyl 1 per cent. Unilateral tarsorrhaphies were performed and opaque patches placed over the closed lids. The animals were dark-adapted for 30 min., after which time they were placed prone, with their heads maintained in a level position. The uncovered eyes were exposed to an unfocused high-intensity light source at a distance of two in. ($4 \cdot 07 \times 10^4$ cd/m.^{2}) for 15 min. The cats were killed by an intracardiac injection of pentobarbital sodium. The lids were dissected free, and the globes gently enucleated and processed in the same way as the rat eyes.

During our experiments, fundoscopy was performed when feasible. The mounted retinae were examined microscopically, and equivalent areas of paired retinae were photographed. The corresponding sets of photomicrographs were compared and evaluated using a dual-projector system. The benzidine-stained retinae were also compared with India ink and Niagara blue dye-injected specimens.

Results

FUNDOSCOPY

The retinal vessels in the enucleated eyes of anaesthetized rats revealed only a slight narrowing as compared with their calibre before enucleation. After decapitation, however, fundus examination revealed marked narrowing of the arterioles, and in the veins, aggregates of red cells moving slowly toward the disc ("box-car" effect).

HISTOLOGICAL STUDIES

The vascular pattern of retinae studied by the benzidine technique was similar to that seen in Indian ink preparations. In neither was the filling complete (Fig. 1). It is emphasized that with the benzidine method only the red cells, and not the vessel walls, accept the stain. Red cells were fairly uniformly distributed within the arterioles and venules in both cat and rat retinae, but some of the larger and secondary vessels in the former appeared empty or only partially filled. In the benzidine-stained retina, the stained material is birefringent when subjected to polarized light, and outlines the retinal vessels (Fig. 2).

The superficial and deep capillary beds could be easily appreciated microscopically (Fig. 3). The superficial net was in the plane of the larger vessels. In cleared specimens the deeper bed was clearly seen, and its capillaries were more closely knit than the super-

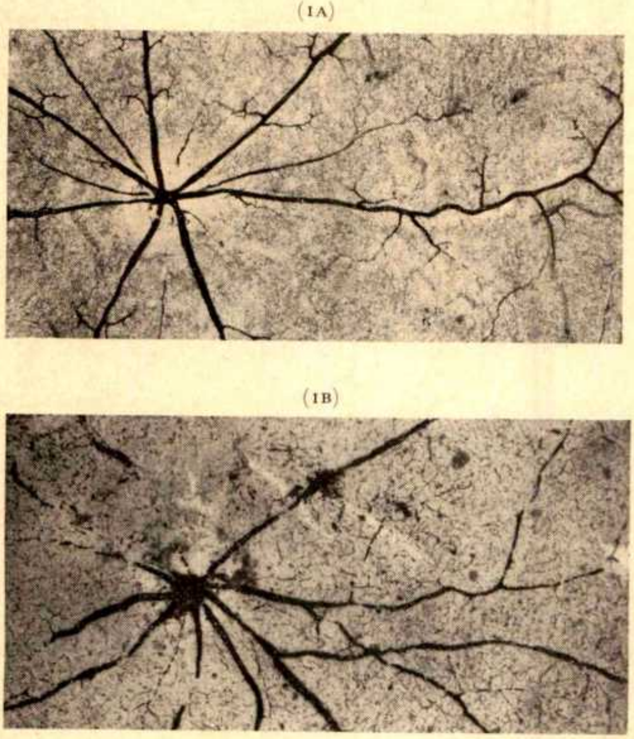

FIG. 1 *Low-power view comparing Indian-ink-injected rat retina* (A) *with benzidine-peroxide stained retina* (B). *Note that in neither instance is vessel filling complete. The stain in* (B) *is specific for red cells.* × 35

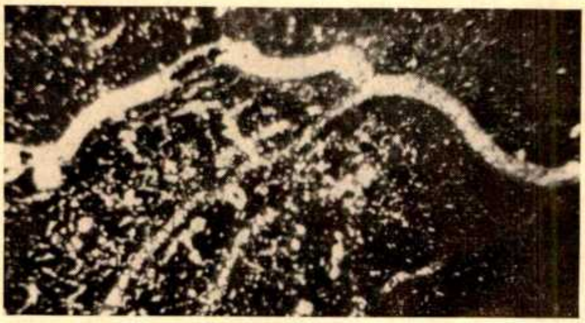

FIG. 2 *High-power view of benzidine-stained cat retina subjected to polarized light. The stained material is birefringent and outlines the retinal vessels.* × 87

ficial net. Most capillaries in both layers contained red cells, not uniformly along the entire channel, but in aggregates of varying length. The channels of the deeper bed appeared more uniformly and more completely filled. However, some capillaries in the mesh appeared empty, especially toward the central areas. In the cat this was particularly apparent near the macular region. In most cases, the peripheral vessels appeared to be broader and better filled with blood (Figs 4 and 5). The distance separating the two layers diminished toward the periphery.

By projecting photographs of equivalent retinal areas side-by-side, the relative filling of the capillaries could be compared (Fig. 6). We could detect no significant difference in vessel filling patterns between the dark-adapted and light-stimulated retinae. Nor was any difference detected as a result of pupillary dilatation, tarsorrhaphy, mode of death, head position, or the order in which the eyes were enucleated.

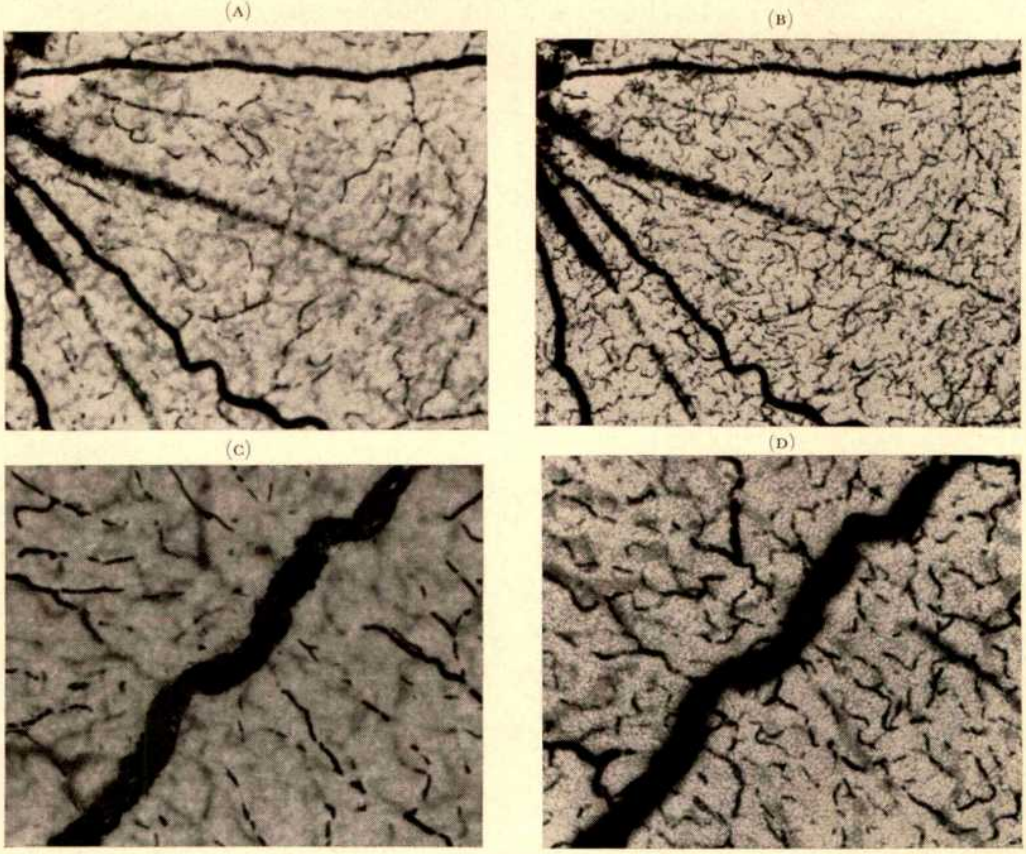

FIG. 3 *Comparison of superficial and deep capillary circulation in a benzidine-stained rat retina under low power* (A *and* B) *and under high power* (C *and* D). *The superficial bed is in the plane of the large vessels. The capillaries contain red cells in aggregates of varying length. The channels of the deeper bed are more uniformly and completely filled and the mesh is more closely knit.* A and B × 82; C and D × 158

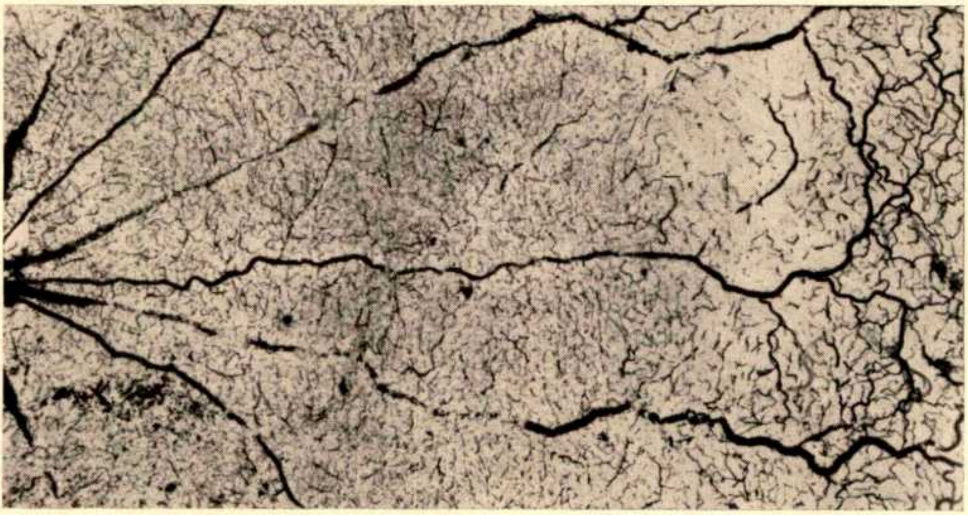

FIG. 4 *Low-power view of benzidine-stained rat retina. The peripheral capillaries appear to be broader and better filled with blood.* × 50

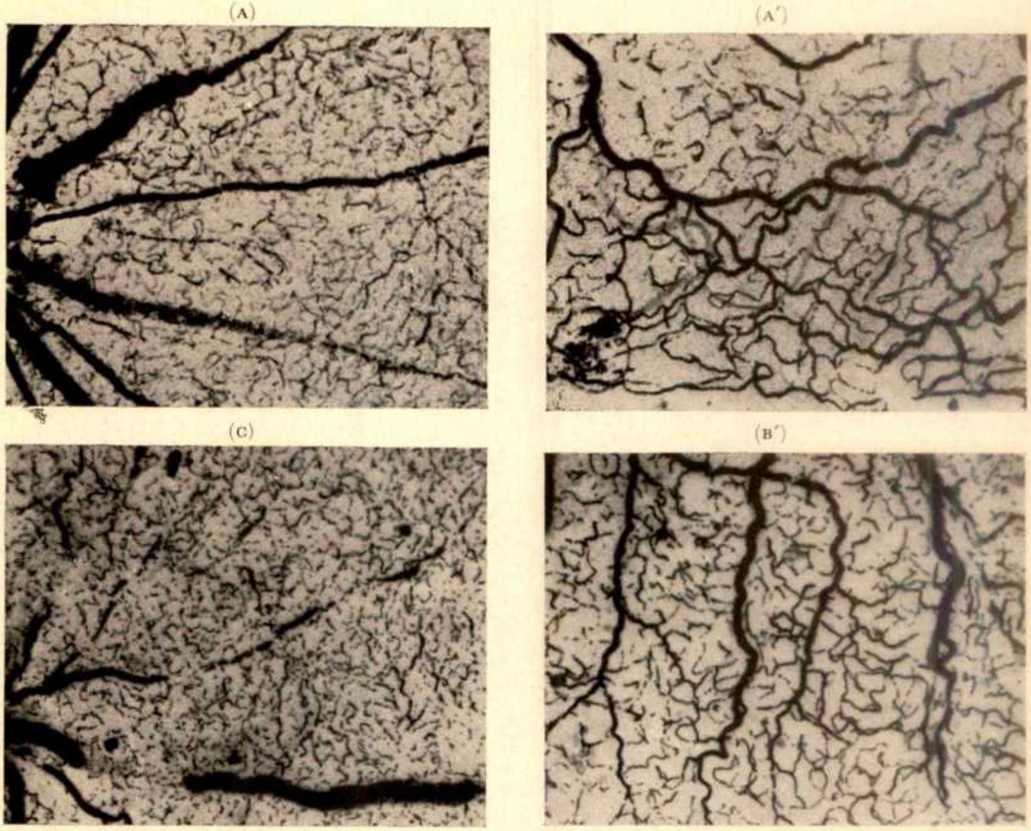

FIG. 5 *Higher-power view of benzidine-stained retina comparing central and peripheral retinal areas.* A and B: *central areas of two rat eyes.* A′ *and* B′: *Peripheral areas of the same two eyes.* × 82

Comment

At the outset of this study we had hypothesized that the vascular response of the light-stimulated retina might be distinguishable from that of the dark-adapted retina by a greater number of capillaries filled with red cells, by fewer spaces within the capillaries which did not contain red cells, or by the presence of more red cells within a widened lumen. In other words, we focused our attention on alterations in blood volume rather than in blood flow.

Several methods of stimulating the uncovered eye were used: exposure to room light for 30 minutes, exposure to an unfocused high-intensity light source for 15 minutes, and exposure to a strobe light flashing at twenty times per second for 30 seconds. The first type of exposure was considered the most physiologic, and the other two were employed to ascertain the possible long- and short-term effects of bright light on the circulation.

We were unable to demonstrate any significant differences in the vascular filling pattern in paired retinae subjected to the conditions of the experiments. It is, of course, possible that subtle differences between the light-stimulated and the dark-adapted state could not be appreciated by visual comparison.

The possibility that such differences might be demonstrated was based on the following considerations:

The retina is essentially an outgrowth of the central nervous system and its vasculature may be anatomically and physiologically similar to the vasculature of brain substance.

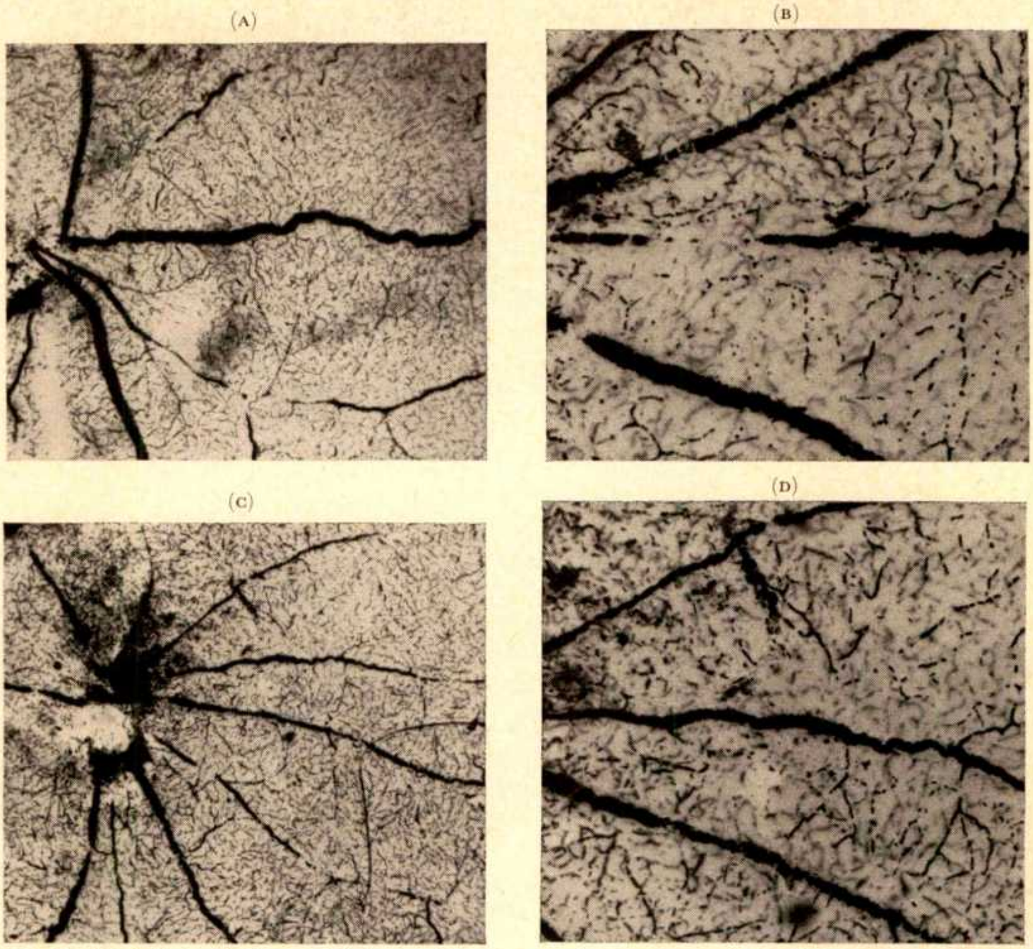

FIG. 6 *Equivalent retinal areas of both eyes of a rat.* A *and* C × 35; B *and* D × 82
A *and* B *represent low and higher power views of the right eye, exposed to light-stimulation*
C *and* D *are equivalent areas of the left eye, which was dark-adapted*

There is substantial indirect evidence for the concept that alterations in the metabolic requirements of brain cells in man have an effect on the vascular response (Cobb and Talbott, 1927; Dunning and Wolff, 1937; Craigie, 1938; Serota and Gerard, 1938; Landau, Freygang, Roland, Sokoloff, and Kety, 1935). In this regard, Jacobson and Basar (1956) and others have shown that any one of several vasodilators causes a marked increase in the amplitude of the scotopic *b*-wave in normal individuals. This suggests some relationship between the amplitude of the *b*-wave, which is thought to be generated by the bipolar cells (inner nuclear layer), and increased blood flow to the area. Further, Nichols, Jacobowitz, and Hottenstein (1967) demonstrated localized histochemical differences in the inner plexiform layer (an area supplied by the retinal circulation) in the light- and dark-adapted state.

It has been shown that the brain is continually active under normal circumstances. The dark-adapted retina also maintains a high level of "spontaneous" electrical activity as shown by Kuffler (1953) and others, using microelectrodes. The rate of retinal blood flow necessary to support this activity is about three times the rate for the brain as a whole, and most closely approaches the highest regional flow rate of 180 ml./100 g./min. in the inferior colliculus (Hickam and Frayser, 1966). From the available evidence (Lennox, Gibbs, and Gibbs, 1938; Kety, 1960; Sokoloff, 1960), it is felt that the overall metabolic rate in the brain can be maintained independent of blood flow over a wide range; an increased flow, for example, would result only in a decreased arteriovenous difference for nutrients and metabolites. It would appear, then, that the total circulation in both brain and retina is fairly constant. This does not preclude the possibility that altered nutritional requirements can trigger localized vascular changes which would cause local variations in flow. Although we were unable to demonstrate these localized changes in the vasculature of paired retinae, we made some interesting observations about the filling pattern of the retinal vessels as demonstrated by the benzidine-staining technique.

This technique has been previously used to study retinal vessels (Michaelson, 1954; Keeney and Barlow, 1956; Thuránszky, 1957). Michaelson (1954), in studying retinal vascular patterns, reinforced the natural blood content of the vessels by injecting a gelatin solution of sedimented red cells. It has been stated that one disadvantage of the benzidine technique is that many capillaries are either incompletely filled or become emptied of blood in the course of processing. We did not find the latter to be true, and the former is not a disadvantage when the purpose is to examine the distribution of red blood cells and not the vessels *per se*. In so doing, our findings were essentially in accord with the studies *in vivo* of Thuránszky (1957), and Keith, Cunha-Vaz, and Shakib (1967), who removed the anterior segment of the cat eye and observed the circulation using a microscope with a water objective. They found that most of the central capillaries appeared and disappeared, with red cells passing through these vessels in clumps. (Evidence that capillary closure does not account for the discontinuous flow of red blood cells was provided by Dollery, Henkind, Kohner, and Paterson (1968), whose fluorescein ciné-angiography studies in pigs indicated that at least plasma was always present in almost all capillaries.) Other larger capillaries, having a fairly direct route from arteriole to venule, had an almost constant flow of red cells. On the basis of the present study, we can make no statement on the preferential pathways described by these workers. However, we did find that some capillaries devoid of red cells are present at the posterior pole of the cat retina, and that in the cat and rat retinae red cells grouped in discontinuous aggregates are present within most other capillaries. The peripheral vessels appear to be better filled with blood in most cases. Thuránszky (1957) felt that they were shunt vessels, and Keith and others (1967) noted their presence in Indian-ink-injected rat retinae.

Michaelson (1954) had reported that the deep retinal capillary bed consists of a denser meshwork than the superficial bed, and that, at least in the rat, it is essentially venous in nature. In this regard, it is of interest that Cunha-Vaz (1966) found that, by inducing a temporary stasis in the retinal vessels of albino rats, permeability changes were produced within the deep capillary net, extending later to the larger venules. In addition to confirming the relatively greater density of the deeper net, we were able to show that the latter had consistently greater red cell filling than the superficial net. This might be expected if the deep bed were on the venous side of the circulation. However, it could also conceivably be the result of an increased regional metabolic requirement.

In our study, we were attempting to examine the circulatory pattern at isolated moments in time; the situation being analogous to looking at a single frame of a ciné film. One cannot assume that blood flow is constant, or that the total flow varies with the anatomical size of the bed. Blood flow itself may not necessarily be proportional to metabolic requirements since oxygen uptake may vary, and blood flowing through shunts may be poorly utilized. Dunning and Wolff (1937) have shown that the vascularity of the cerebral cortex is about twice that of peripheral nerves, but oxygen consumption is about 30 : 1. Thus anatomical findings may be only roughly indicative of metabolic requirements.

Artefact must also be considered in the interpretation of our results, and this includes possible agonal or *post mortem* changes in red cell content or vessel calibre. Since the histological appearance of the benzindine-stained retina basically reflects the pattern *in vivo*, however, it is our feeling that, with careful handling of the material, the red cell distribution within the microcirculation is not greatly altered in processing. Because of this, and because of the simplicity of the benzidine technique, it may prove a useful adjunct in the study of retinal microcirculatory patterns and responses.

Summary

The effects of light-stimulation and dark adaptation on the quantity and distribution of red blood cells within the retinal vessels were studied. Using the benzidine-peroxide staining techniques, in which only red blood cells accept the stain, we were able to compare pairs of flat-mounted animal retinae by photographing equivalent areas and projecting them side-by-side. Although no demonstrable difference in the vascular filling pattern was found between the two states, it was shown that the red cell distribution *in vitro* in the examined retinae mirrored the findings of various techniques *in vivo*. It was felt that the benzidine-peroxide staining method may prove a useful adjunct in the study of patterns and responses of the retinal microcirculation.

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Ocular leprosy in Malawi

Clinical and therapeutic survey of 8,325 leprosy patients

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Ocular involvement in leprosy is reported to be very common: Harley (1946) 30 per cent.; Kirwan (1955) up to 100 per cent.; Landau and Gabbay (1955) 90 per cent.; Woods (1961) 60 to 90 per cent. The eye lesions may be due to direct infection by *Mycobacterium leprae*, to exposure and secondary infection consequent to Vth and/or VIIth cranial nerve palsy, or to a sensitivity reaction to leprous activity elsewhere in the body.

Since the introduction of the sulphones, most cases of leprosy are amenable to treatment. The value of sulphones in the treatment of ocular leprosy and of steroids in leprous reactions are well known, although no full statistical data is available.

The incidence of leprosy in Malawi is one of the highest in the world according to the World Health Organization (1958), and there were 8,325 registered patients in Southern Malawi in October, 1968. We surveyed all these patients in order to determine the prevalence of ocular involvement, to describe the eye manifestations, and to assess the therapeutic influence of sulphones and steroids on the ocular lesions.

Material and methods

Patients affected by leprosy were examined in the villages (from mobile units),* in dispensaries, and in leprosaria.

Of the 8,325 registered patients, 7,653 were registered in the villages, 190 in the dispensaries, and the rest in the leprosaria. All were examined either by a leprosy specialist or by a well-trained medical assistant. The Vth and VIIth cranial nerve function and the condition of the anterior segment of the eye were carefully examined. Scrapings were taken for bacteriological examination. Recordings were made (on IBM cards) of the clinical manifestations of the lesions, duration of disease, and treatment. The disease was classified according to the clinical manifestations and the presence of bacilli into the three groups. Lepromatous type was recorded when the profuse areas of granulation tissue contained bacilli. Tuberculoid type was recorded when the lesions were relatively stable and localized and bacilli seldom found. Borderline cases were those in which the clinical appearance was intermediate between the lepromatous and tuberculoid types. The smears in these cases were sometimes mildly positive.

Affected patients were sent by the leprosy specialist or medical assistant to Queen Elizabeth Central Hospital, Blantyre, where they were examined by two ophthalmologists. Ophthalmoscopy, if the state of the media allowed, and slit-lamp examination were performed. If necessary the patients were admitted into the leprosy or the eye department.

An eye was considered to be blind when the corrected visual acuity was 3/60 or below.

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*Four mobile L.E.P.R.A. clinics based at the Lepra Control Centre, Blantyre.

Results

5,827 patients (70 per cent.) had tuberculoid leprosy, 1,914 (23 per cent.) were lepromatous, and 582 (7 per cent.) were borderline cases. Of the 8,325 patients, 532 (6·3 per cent.) had ocular lesions (203 lepromatous, 250 tuberculoid, and 79 borderline: Table I).

Thirty eyes (0·3 per cent. of the 8,325 patients) were found to be blind; twenty of these eyes were lepromatous, eight tuberculoid, and two borderline. The prevalence of ocular manifestations in the three types of leprosy is summarized in Table I.

Table I *Findings* in 532 leprosy cases with ocular change, by type of leprosy*

	Eye conditions											
Type of leprosy	*All*		*Corneal anaesthesia*		*Lagophthalmos*		*Keratitis*		*Iridocyclitis*		*Blind*	
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Lepromatous (1,914)	203	11·0	55	2·9	50	2·6	36	1·8	129	6·7	20	1·0
Borderline (582)	79	14·0	26	4·5	23	4·0	4	0·7	9	1·5	2	0·4
Tuberculoid (5,827)	250	4·3	167	2·9	198	3·4	47	0·8	5	0·1	8	0·1
Total (8,325)	532	6·3	248	3·0	261	3·1	87	1·0	143	1·8	30	0·3

* Multiple findings are included separately

There was a difference in ocular involvement in the three types. Most of the cases of iridocyclitis were found in cases of lepromatous leprosy, while most cases of corneal anaesthesia and lagophthalmos were found in the tuberculoid group. The prevalence of iridocyclitis in the borderline group was intermediate between that in the lepromatous and tuberculoid groups.

130 patients (24 per cent.) with ocular complications were known to have been affected by leprosy for periods of less than 5 years, while in 402 cases* (76 per cent.) the disease was of longer duration. This shows a correlation between the overall prevalence of ocular findings and the duration of the disease. The tuberculoid cases tended to show ocular lesions earlier than the lepromatous ones (Table II), sometimes even in the first months of the disease.

Table II *Duration of leprosy in 532 patients with ocular lesions, by type of leprosy*

Duration (yrs)		*Under 5*		*Over 5*	
		No.	*Per cent.*	*No.*	*Per cent.*
Type of leprosy	Lepromatous (203)	30	15	173	85
	Borderline (79)	25	32	54	68
	Tuberculoid (250)	75	30	175	70
	Total (532)	130	24	402	76

Among the 203 lepromatous cases with ocular lesions, 170 (74 per cent.) were untreated; only twelve (6 per cent.) presented ocular lesions while under dapsone treatment. The rest (20 per cent.) had formerly been treated but the treatment had been discontinued.

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*The duration recorded was, in general, derived from the patient's statement, except in cases where it differed grossly from the clinical manifestations, in which case an estimate was made.

Among the 250 tuberculoid cases with ocular lesions, 85 (34 per cent.) were untreated and 102 (41 per cent.) were receiving appropriate systemic treatment (Table III).

Table III *Effect of treatment on prevalence of ocular manifestations, by type of leprosy*

Treatment		*Untreated*		*Formerly treated*		*Currently treated*	
		No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
Type of leprosy	Lepromatous (203)	150	74	41	20	12	6
	Borderline (79)	32	41	29	37	18	22
	Tuberculoid (250)	85	34	63	25	102	41
	Total (532)	267	50	133	25	132	25

CLINICAL MANIFESTATIONS

The ophthalmic division of the Vth cranial nerve is affected mainly in the tuberculoid type and results in corneal and conjunctival anaesthesia. Vth nerve involvement was found in 248 patients, of whom only 47 had neuroparalytic KERATITIS.

Palsy of the superior division of the VIIth cranial nerve leads to LAGOPHTHALMOS. This was present in 251 (47 per cent.) of patients with ocular manifestations, 198 (79 per cent.) of the tuberculoid and forty (20 per cent.) of the lepromatous patients being affected. Most of these patients had previously been known to be borderline or tuberculoid cases.

In a few patients a mechanical lagophthalmos was produced by lid infiltration by a lepromatous mass. In one of these, the infiltration, proved histologically, occurred in the lower lid; this has not previously been demonstrated.

CORNEAL INVOLVEMENT was found in 87 patients, 47 affected by exposure keratitis and forty presenting superficial punctate keratitis. In five cases there was PANNUS FORMATION around the whole circumference, resembling an exaggerated arcus senilis (Fig. 1).

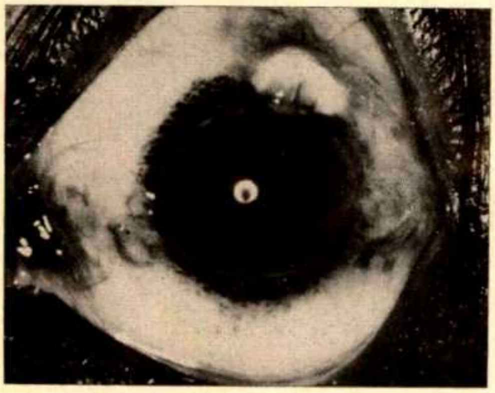

FIG. 1 *Lepromatous leprosy. After filtering operation for glaucoma. Note pannus formation circling the cornea resembling arcus senilis*

IRIS AND CILIARY BODY INVOLVEMENT was a common finding in the lepromatous group and proved to be the main cause of BLINDNESS. It was found in 129 (63 per cent.) of this group. The path of invasion is still uncertain. It could be due to a bacillaemia which is known to be present in the acute reactions, or to invasion through the branches of the Vth nerve. Direct spread from neighbouring structures is unusual. The iridocyclitis is, however, probably usually due to a uveal sensitivity to leprous breakdown products elsewhere in the body. It can appear spontaneously, or after a new drug is started, and this should be taken into account. It is usually controlled with corticosteroid treatment and with it recovery may be obtained even in desperate cases.

Two types of IRIDOCYCLITIS were found:

(*a*) *Chronic plastic iridocyclitis* The eye remains completely quiet and synechiae form, leading sometimes to seclusion of the pupil. Lens opacities are common in such cases. In a few cases miliary iris lepromata are found at the pupillary margin, while larger iris nodules are found elsewhere on the iris.

(*b*) *Acute diffuse iridocyclitis* This condition, which is usually bilateral, has a clinical course characterized by relapses and remissions. Lid swelling, circumcorneal congestion, keratic precipitates, and a plastic unorganized exudate are present. The plastic exudate may fill the anterior chamber. The viscous nature of the exudate permits it to accumulate in the angle of the anterior chamber, without necessarily being affected by gravity (see Fig. 2).

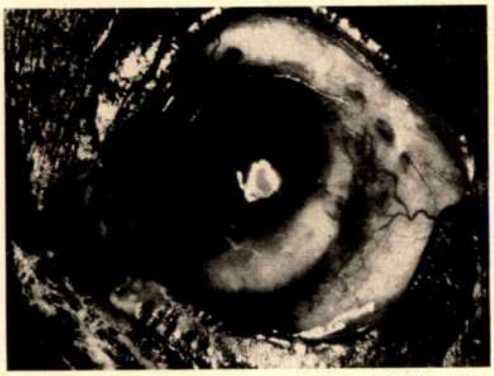

FIG. 2 *Lepromatous leprosy. Plastic iridocyclitis with a viscous exudate not influenced by gravity*

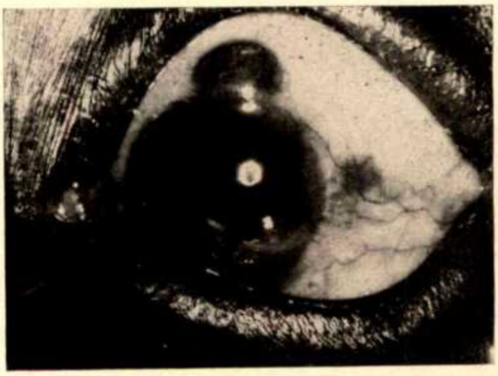

FIG. 3 *Lepromatous leprosy. Plastic iridocyclitis with spontaneous scleral perforation and subconjunctival uveal prolapse accompanied by a filtering bleb*

The iridocyclitis resulted in GLAUCOMA in four patients.

In one lepromatous patient a spontaneous SCLERAL PERFORATION took place near the limbus. A subconjunctival iris prolapse developed, accompanied by a filtering bleb, which resulted in lowering of the previously raised ocular tension (Fig. 3).

If the media allowed, the fundus was examined in the patients who were referred because of lid, conjunctival, corneal, and anterior segment lesions. Occasionally non-specific peripheral CHOROIDITIS was found, but choroiditis was not found at the posterior pole as previously reported by Siqueria de Carvalho (1948) and Aparisi (1950).

Discussion

The presence of ocular involvement in 6·3 per cent. and of blindness in 0·3 per cent. of 8,325 patients with leprosy is very low in comparison with the figures reported by Harley (1946), Kirwan (1955), Landau and Gabbay (1955), and Woods (1961).

Two factors must be considered in investigating ocular involvement in leprosy.

(**1**) Duration of disease, to which the ocular affection was found to be in direct relation. Of the 532 patients with ocular manifestations, 402 (76 per cent.) had had leprosy for more than 5 years. The duration of disease was of greater significance in the lepromatous than in the tuberculoid cases. Some tuberculoid cases were found to have eye complications even after a few months, while in lepromatous cases the eyes were never affected until 2 to 3 years had passed. This is probably related to the slow intraocular invasion of lepra bacilli in lepromatous cases; secondary infection superimposed on cranial nerve lesions in tuberculoid cases occurs sooner.

(2) Systemic treatment. Of the 532 affected cases, 267 (50 per cent.) were untreated and only 25 per cent. were being currently treated. This appears to suggest that systemic treatment helps to prevent ocular involvement. The difference in prevalence of eye lesions between this report and those presented 10 years ago is due to the recent wide use of sulphones. The therapeutic effect of sulphones was found to be higher in lepromatous than in tuberculoid cases. Only 6 per cent. of the lepromatous cases with eye manifestations were currently receiving treatment compared with 41 per cent. of the tuberculoid patients. The sulphones have a specific bacteriostatic effect which prevents intraocular invasion by lepra bacilli, but have no influence on secondary infection superimposed on cranial nerve palsy in tuberculoid cases.

Summary

The ocular condition in 8,325 Malawi leprosy patients was surveyed; 6·3 per cent. were found to suffer from eye lesions and only 0·3 per cent. were blind.

The patients are classified into lepromatous, borderline, and tuberculoid groups. In lepromatous patients eye lesions occur in the later stages of the disease, and in tuberculoid patients at an earlier stage. Lepromatous patients are affected mainly by iridocyclitis and superficial punctate keratitis. Tuberculoid patients suffer mainly from lagophthalmos and corneal anaesthesia due to nerve palsy (Figs 4 and 5).

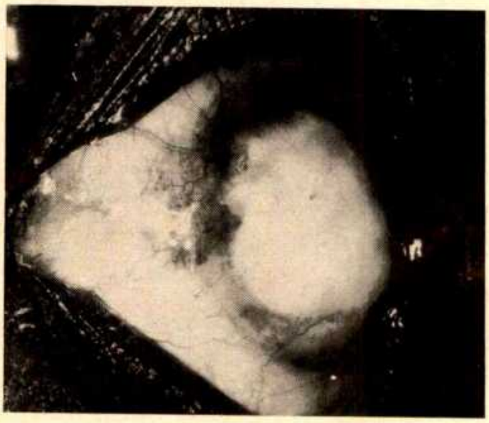

FIG. 4 *Tuberculoid leprosy. Total leucoma due to exposure and corneal anaesthesia*

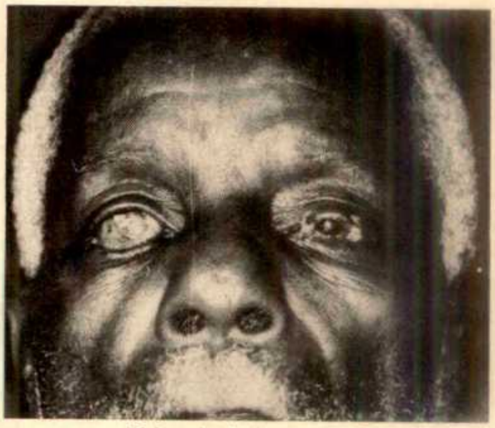

FIG. 5 *Tuberculoid leprosy. Lagophthalmos due to VIIth cranial nerve palsy. Left eye post-tarsorrhaphy*

The low incidence of ocular manifestations is considered to be due in part to the wide use of sulphones; this is especially true in the lepromatous group, in which only 6 per cent. had eye lesions while under dapsone treatment. In tuberculoid patients under current treatment eye manifestations were present in 41 per cent.

Steroids are highly effective in controlling hypersensitivity reactions of the uvea.

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Pyrrolidinomethyl tetracycline in cavernous sinus thrombosis

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Before the advent of antibiotics, cavernous sinus thrombosis of septic origin was invariably fatal (Grove, 1936). After the introduction of sulphonamides and antibiotics, Shaw (1952) collected from the literature sixty cases of cavernous sinus thrombosis in which these drugs were used, and observed that the mortality rate had come down to 11·7 per cent., but that 77 per cent. of those who survived showed residual abnormalities. Clune (1963) reported a survival rate of 72 per cent. with a 50 per cent. morbidity rate in those who recovered. In an attempt to reduce the high morbidity rate in survivors, newer antibiotics and anti-inflammatory and anti-thrombotic agents have been tried in various combinations. The present study reports our experience of treating seven cases of septic cavernous sinus thrombosis with pyrrolidinomethyl tetracycline (Reverin).

This is a pyrrolidinomethyl derivative of tetracycline with the molecular formula $C_{27}H_{33}O_8N_3$. It is a water-soluble compound which can be administered intravenously or intramuscularly; it quickly attains high and reliable blood concentrations and the normal intestinal flora are not much affected. After the intravenous injection of 275 mg. Reverin the initial serum concentrations are almost ten times as high as after the oral administration of 250 mg. tetracycline hydrochloride (Strauch and Koch, 1958); 8 hours later the former is still almost twice as high as the latter, and even after 24 hours therapeutic blood levels of Reverin can still be demonstrated (Finland, Purcell, Wright, Del Love, Mou, and Kass, 1954). Dimmling, Huner, Lutzeyer, and Simon (1958) have shown that the potency and bacteriostatic range of Reverin is similar to that of tetracycline hydrochloride, but with a much lower general and local toxicity.

Because of these advantages, it has been extensively used in fulminating infections with encouraging results, and it is therefore surprising that only one previous report of its use in a case of cavernous sinus thrombosis has been found (Khare, 1967).

The usual organisms encountered in cases of cavernous sinus thrombosis are the *Streptococcus*, *Staphylococcus*, *B. proteus*, *B. pyocyaneus*, *Pneumococcus*, and *Meningococcus* (Walsh, 1957). Tempea and Gorun (1959) stated that the first two organisms were most commonly encountered, and Clune (1963) found *Staphylococcus aureus* (coagulase-positive) to be the most frequent.

Reverin is effective against all these organisms (Finland and others, 1954), but sulphonamides and antibiotics, including broad-spectrum tetracycline and chloramphenicol, have not proved to be very effective (Table III, p. 115).

Material and methods

Seven cases of septic cavernous sinus thrombosis were treated with intravenous pyrrolidinomethyl

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tetracycline (Reverin) 275 mg. 8-hrly. Other supportive therapy, including anti-coagulants and Diamox, was added when necessary.

All the patients presented in a semiconscious or unconscious state, with high fever and neck rigidity. The clinical particulars are given in Table I.

Table I *Clinical particulars of seven cases of cavernous sinus thrombosis treated with intravenous Reverin*

Case no.	*Age (yrs)*	*Sex*	*Precipitating cause*	*Latent period (days)*	*General examination*					*Duration of treatment (days)*	*Outcome*
					Appearance	*Blood pressure*	*Temperature (°F.)*	*Leucocyte count (per cu mm.)*	*Erythrocyte sedimentation rate (mm./1st hr)*		
1	40	M	Boil on nose	8	Dehydrated and toxic	112/70	103°	22,000	80	7	Died
2	35	F	Septic abortion	4	Unconscious	100/60	102°	10,000	60	15	Cured
3	20	F	Furuncle on nose	5	Semiconscious	100/70	102°	10,500	101	30	Cured
4	40	F	Acute exacerbation of chronic suppurative otitis media	8	Semiconscious	150/70	103°	19,200	80	20	Cured
5	30	F	Septic abortion	9	Unconscious Flexor plantar reflexes	140/95	104°	20,000	100	5	Died
6	20	F	Abscess on right temple	7	Semiconscious	140/80	104°	12,000	100	24	Cured
7	12	M	Not known	Not known	Semiconscious	110/80	103°	15,400	104	16	Cured

The results of the ophthalmological examination are shown in Table II (opposite). All the patients showed lid oedema and conjunctival chemosis.

Observations

Of the seven patients treated, five (71·4 per cent.) recovered without any residual effects, and two died with cardiorespiratory failure during the acute phase of the illness. The duration of treatment required in the survivors ranged from 15 to 30 days.

Unfortunately the blood cultures taken in our Cases 2, 3, and 4 were sterile. In one case *Staphylococcus saprophyticus* was grown.

Comment

The most significant feature noted in the present series was that there was no evidence of residual damage in the five patients who recovered, whereas previous reports have shown morbidity rates of from 50 to 77 per cent. (Table III, opposite).

We therefore feel that pyrrolidinomethyl tetracycline is the drug of choice in the management of septic cavernous sinus thrombosis, and that it should be administered from the start, without first trying less potent agents.

Table II *Ophthalmological findings in seven patients*

Case no.	*Eye involved*	*Fundus*	*Other observations*
1	Both (left more than right)	Hyperaemic disc Dilated vessels	Proptosis Limitation of movement Mastoid oedema
2	Right	Hyperaemic disc Blurred margins Dilated vessels	Axial proptosis Mastoid and facial oedema Pupils semidilated with sluggish reaction
3	Both (left more than right)	Not visible	Axial proptosis Exposure keratitis Mastoid oedema
4	Both (left more than right)	Normal	Proptosis Limitation of movement Mastoid oedema
5	Right	Hyperaemic disc	Proptosis Limitation of movement Mastoid oedema Pupils semidilated with sluggish reaction
6	Right	Dilated vessels	Proptosis Limitation of movement
7	Left	Hyperaemic disc Retinal oedema Dilated vessels	Proptosis Limitation of movement

Table III *Mortality and morbidity rates in cases reported by other workers compared with the seven cases here reported*

Author	*Year*	*Total cases*	*Mortality (per cent.)*	*Morbidity (per cent.)*
Shaw	1954	60	11·7	77·0
Yarington	1961	878	80·0	75·0
Clune	1963	36	28·0	50·0
		5	60·0	50·0
Present series	1969	7	28·6	Nil

Summary

Pyrrolidinomethyl tetracycline (Reverin) was given intravenously in seven cases of septic cavernous sinus thrombosis, and was found to be useful in eliminating residual morbidity in the five patients who recovered.

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Anterior lens displacement with age

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A slight anterior displacement of the lens with age was first postulated by Raeder (1922). Using a new ophthalmophakometer, he measured the positions of the anterior and posterior lens surfaces relative to the cornea. By graphing the means of the measurements within successive age groups he constructed regression lines for the position of the two lens surfaces against age, but no tests for statistical significance were applied.

In particular, Raeder used the age range from 25 to 65 years and found during that time:

(1) A mean decrease of anterior chamber depth of 0·47 mm.

(2) A mean increase of lens thickness of 0·81 mm.

(3) A forwards displacement of the anterior lens surface of 0·33 mm.

(4) A backwards displacement of the posterior lens surface of 0·20 mm.

All these figures cannot be reconciled, but comparing (1) and (2) together and then (3) and (4) together, a slight anterior lens displacement with age is indicated.

Raeder's graph for age *v.* posterior lens surface position looks unsatisfactory, and Raeder admitted that the posterior lens measurements were less exact than the anterior.

Raeder's observations of lens displacement with age have attracted very little interest over the years (Calmettes, Deodati, Huron, and Béchac, 1958; Weale, 1962), and his examinations do not appear to have been repeated.

With time-amplitude ultrasonography the positions of the various interfaces in the eye can be readily measured. The detailed procedure and the accuracy of the method have been previously described (Lowe, 1967, 1968).

Technique and subjects

Eighty people with normal eyes, 57 females and 23 males, aged between 30 and 85 years (mean 61·2), were referred from the hospital's outpatient department. Most had attended for presbyopic corrections and none had high refractive errors although they were not selected for emmetropia. Both eyes were used as a means of cross-checking the technical aspects of the procedures, but tests from three eyes were rejected because of unsatisfactory recordings. These 157 normal eyes were the same as those used for other tests previously reported (Lowe, 1967, 1968, 1969a, b, c). Pupils were dilated with 2 per cent. homatropine and cocaine eyedrops.

15 MHz time-amplitude ultrasonography with a stand-off technique was used (Lowe, 1967). The method has been shown to be sufficiently accurate for biometric population studies (Lowe, 1968).

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Results

These are summarized in the Table.

Table *Summarized statistics for age (X) v. various parameters (Y) of 157 normal eyes*

Parameter (Y)	*Regression line slope*	*Change in 50 years (mm.)*	*Analysis of variance*		
			F-ratio	*Probability*	*Significance*
Central corneal thickness	+0·0002	+0·01	1·17	0·70 > P > 0·90	not
Mean corneal radius	−0·0005	−0·025	0·100	> 0·50	not
Axial length	−0·00085	−0·04	0·030	≯ 0·50	not
Anterior chamber depth	−0·013	−0·65	47·01	> 0·9995	extremely
Half lens thickness	+0·0073	+0·365	80·45	> 0·9995	extremely
Lens thickness + vitreous length	+0·011	+0·55	7·30	0·99 > P > 0·995	extremely
Corneal thickness + anterior chamber depth + lens thickness	+0·0017	+0·085	0·93	0·50 > P > 0·70	not
Vitreous length	−0·0025	−0·125	0·29	≯ 0·50	not
Anterior chamber depth + half lens thickness	−0·0025	−0·125	1·86	0·70 > P > 0·90	not

Corneal thickness, corneal radius of curvature, and axial length showed no significant change with age (Lowe, 1969a, b, c), so that the corneal surfaces and "retina" could be considered fixed reference points for measurements of the lens changes.

"t"-tests were applied to selected pairs of regression coefficients of appropriate parameters (Y) against age (X) in order to compare the magnitudes of the two factors with increasing age. The signs of the regression coefficients were neglected in these tests.

The position of anterior lens surface in relation to age was measured from two directions—the distance from back of cornea to front of lens (anterior chamber depth) and the distance from front of lens to retina (lens thickness + vitreous length) (Table). A "t"-test showed no significant difference between the magnitudes of the two regression coefficients (t = 0·410; degrees of freedom = 310). The mean decrease in anterior chamber depth for 50 years was 0·65 mm. which was not statistically different from 0·55 mm. for the mean increase in the distance from anterior lens surface to retina.

The mean change in posterior lens surface position in relation to age was also measured in two directions—the distance from front of cornea to back of lens (corneal thickness + anterior chamber depth + lens thickness) and the distance from back of lens to retina (vitreous length) (Table). A "t"-test showed no significant difference between the magnitudes of these two regression coefficients (t = 0·853; degrees of freedom = 310).

The mean change in posterior lens position in 50 years was 0·085 mm., measured from the front of the cornea to the back of the lens, which showed no statistical difference from 0·125 mm. measured from back of lens to retina.

Biomicroscopy and histology show that the lens grows symmetrically antero-posteriorly. If there were no change in lens position with age, the shallowing of anterior chamber depth should be equal to half the increase in lens thickness. A "t"-test was applied to the magnitudes of the paired regression slopes of age *v.* anterior chamber depth, and age *v.* half lens thickness (Table). A highly significant difference was found (t = 2·75; d. of f. =

310; $0{\cdot}97 > P > 0{\cdot}999$). The regression slopes show that anterior chamber depth decreases more quickly than half lens thickness increases, indicating another factor in addition to lens thickness as a cause of diminishing anterior chamber depth. Comparison of the rates of change shows that the additional factor has less influence on anterior chamber depth than the lens growth.

Likewise a "*t*"-test applied to the magnitudes of the regression slopes for age *v.* half lens thickness, and age *v.* corneal thickness + anterior chamber depth + lens thickness (position of posterior lens surface) (Table) showed an extremely significant difference ($t = 2{\cdot}88$; d. of f. = 310; $0{\cdot}995 > P > 0{\cdot}999$).

The change in the position of the posterior lens surface is not equal to half the additional lens thickness but is considerably less (Table) because the posterior displacement of the posterior lens surface that would be produced by lens growth is reduced by another factor (anterior lens displacement).

Thus, the position of the anterior lens surface moved more anteriorly than half the increase in lens thickness caused by lens growth, and the position of the posterior lens surface moved less posteriorly than half the increase in lens thickness caused by lens growth.

Finally, a "*t*"-test was applied to the magnitudes of the regression slopes for age *v.* anterior chamber depth, and age *v.* vitreous length. An extremely significant difference was found ($t = 4{\cdot}35$; d. of f. = 310; $0{\cdot}999 > P$). The regression slopes showed that with age the position of the anterior lens surface (anterior chamber depth) was changing much faster than the position of the posterior lens surface (vitreous length).

The distance of anterior chamber depth + half lens thickness was measured as an indicator of central lens position. This is a more difficult and less exact calculation than the measurements of the other distances because it involves combining two separate ultrasonic measurements, one of which is obtained by halving the distance between two ultrasonic reflexes. The change was found to be $-0{\cdot}125$ mm. for 50 years and although the change in direction (forwards) is consistent with the previous figures, the slope of the regression line failed to achieve statistical significance. This lack of statistical significance is not surprising in view of the relatively small amount of lens displacement in 50 years in relation to the measuring method.

Comment

Slit-lamp examination and histological experience show an equal antero-posterior growth of the lens during adult life and not a crowding of the new lens fibres into the anterior portion of the lens. The figures in the Table show a considerably increased change in the position of the anterior lens surface compared with the posterior lens surface (0·65 mm./0·13 mm. in 50 years). These figures indicate 0·2 mm. anterior displacement of mid-lens position in 50 years, which is within clinical range of the figure of 0·125 mm. shown in the Table.

Discussion

Cause of anterior lens movement with age

Priestley Smith (1883) was the first to demonstrate conclusively the overall increase in lens size throughout life. The lens growth he postulated is no longer disputed.

The zonule must be a relatively inelastic structure to convert ciliary body changes into alteration of less form. During accommodation, the lens is displaced slightly by gravity, and anterior lens movement is very marked following zonulolysis before cataract extraction. Likewise, increase of equatorial diameter and antero-posterior thickness of the lens with age can be expected to cause a slackening of the zonule which could be taken up by anterior lens displacement.

Clinical conditions

The investigations described in this paper were undertaken to determine if anterior lens movement with age might have any significant role in the production of the shallow anterior chambers of primary angle-closure glaucoma.

In a lifetime, the change in lens position is very small in relation to the mean difference of 1·0 mm. between the anterior chamber depths of normal eyes and eyes with primary angle-closure glaucoma. Normal anterior lens displacement with age would not be a factor in causing the shallow anterior chamber of eyes affected with primary angle-closure glaucoma except in exceptional cases in some very elderly people where the lens displacement could be added to the other lens factors (Lowe, 1969a).

Weale (1962) has discussed the effects on physiological optics of anterior lens movement with age.

Accuracy of measurements

Anterior chamber depths have been measured by a large number of investigators and regression lines for decrease of anterior chamber depth with age have been given by Raeder (1922), Rosengren (1931, 1950), Tornquist (1953), Calmettes and others (1958), Weekers, Grieten, and Lavergne (1961), Luyckx-Bacus and Weekers (1966), and Lowe (1968). Their results are surprisingly inconsistent. Part of the differences probably depend upon variations in population samples. Most authors stated their patients were emmetropic, but this state is difficult to define in elderly people. Part of the differences probably depend upon different instrumentation as well as errors from the calculations which are based on standard eyes.

Time-amplitude ultrasonography has considerable advantages over optical methods for measuring lens size and position in that mathematical assumptions are less and the position and thickness of the lens can be plotted simultaneously. A limiting factor is the relatively coarse ultrasonic wave-form compared with light.

Ultrasonic ocular biometry is now being used extensively and some large examination series are being compiled. With large numbers and refinements in technique, the results may become more accurate and the small anterior lens movement with age may be capable of more definite direct measurement.

Summary

Ultrasonic biometry indicates a small anterior displacement of the lens with advancing age throughout adult life. The change in lens position is approximately 0·2 mm. in 50 years. Normal anterior lens displacement has very little significance for primary angle-closure glaucoma.

These investigations formed part of Research Projects No. 13 of The Royal Victorian Eye and Ear Hospital, and No. 14 of The Ophthalmic Research Institute of Australia, and were conducted in the Glaucoma Unit of the Hospital. Valuable clinical and technical assistance was given by Dr. Magda Horvat, and the statistics were analysed by Mr. Kenneth Shankly M.Sc. with the computer in the Biophysics Section of the Physiology Department of the University of Melbourne Mrs. G. Heinze translated Raeder's paper.

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Applanation ocular tension in myopia and emmetropia

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Many factors determine the individual intraocular pressure in a given eye and the mean level in a given population. When it is estimated by indentation tonometry, such variables as the corneal curvature and rigidity, the scleral rigidity, and the initial ocular volume, have all been found to influence the readings (Friedenwald, 1937; Phillips and Quick, 1960), but these are much less important when applanation tonometry is used because of the small volumetric displacement (Goldmann, 1957; Schmidt, 1959).

Friedman (1966) showed that differences in the initial volume of the eye affect the stress–strain relationship in the ocular coats, and this may cause variations in tonometric readings, even when the applanation method is used.

Direct determination of the volume of the living eye is difficult but, as there is known to be a correlation between the refraction of the eye and its axial length (and therefore its volume) (Sorsby, Benjamin, Davey, Sheridan, and Tanner, 1957), errors of refraction may influence applanation readings.

The aim of this paper is to report the results of a comparison of applanation tonometric readings in 760 emmetropic and myopic eyes examined at Ain Shams University Hospitals during the year 1967.

Material and methods

Subjects were selected from patients attending the ophthalmic out-patients clinic for refraction and from normal persons accompanying their sick relatives. They were all above the age of 10 years, and their eyes were healthy with no corneo-scleral damage past or present that might have interfered with the measurement of the intraocular pressure.

After the visual acuity had been assessed, the ocular tension was measured with the Goldmann applanation tonometer mounted on the Haag-Streit 900 slit lamp. Homatropine 2 per cent. was then instilled into each eye and one hour later a refraction was done and the results recorded. All eyes with an applanation reading above 20 mm. Hg or below 10 mm. Hg were excluded from the study.

All those examined were divided into five age groups and these were subdivided according to the state of refraction (Table I, opposite):

(*1*) *Emmetropia:* less than ±2 D sph.

(*2*) *Myopia 1:* moderate myopia ranging from −2 D to −6 D sph., with astigmatism less than 2 D cyl.

(*3*) *Myopia 2:* more than −6 D sph., with astigmatism less than 2 D cyl.

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Table I *Distribution of 760 subjects by age group and refractive error*

Age group (yrs)	*Emmetropia*	*Myopia*		*Total subjects*
		1	2	
11–20	75	39	18	132
21–30	90	19	25	134
31–40	148	19	28	195
41–50	144	11	34	189
Above 50	78	17	15	110
Total subjects	535	105	120	760

Results

The data were analysed statistically to determine whether there was any significant correlation between the refractive state and the mean applanation readings in each group. The mean tensions in myopic and emmetropic eyes were compared and Student's "t" test was applied to determine whether the differences were significant (Table II).

In all age groups the mean values for applanation tensions in myopes were higher than in emmetropes, but the differences were not always significant in all age groups. These findings are clearly apparent in Table II.

Table II *Mean ocular tension (mm. Hg), by age group and refraction*

Age group (yrs)	*Refraction*	*No of subjects*	*Ocular tension (mm. Hg)*			*Comparison of myopic with emmetropic eyes*		
						"t" value		*Significance*
			Mean	*SD*	*SE*	*Calculated*	*Tabulated*	
11–20	Emmetropia	75	14·05	±2·24	±0·26			
	Myopia 1	39	**15·73**	±1·92	±0·31	**3·93**	3·37	P < 0·001*
	Myopia 2	18	14·61	±2·58	±0·61	0·92	1·98	P > 0·05
21–30	Emmetropia	90	13·72	±2·40	±0·25			
	Myopia 1	19	14·53	±1·44	±0·33	1·45	1·98	P > 0·05
	2	25	14·48	±2·62	±0·52	1·40	1·98	P > 0·05
31–40	Emmetropia	148	14·19	±2·01	±0·11			
	Myopia 1	19	14·70	±2·14	±0·49	1·03	1·96	P > 0·05
	2	28	**16·58**	±2·32	±0·44	**5·60**	3·29	P < 0·001*
41–50	Emmetropia	144	14·39	±2·22	±0·19			
	Myopia 1	11	**16·05**	±2·83	±0·85	**2·32**	1·96	P < 0·05*
	2	34	**15·33**	±2·69	±0·46	**2·12**	1·96	P < 0·05*
Over 50	Emmetropia	78	14·87	±1·88	±0·21			
	Myopia 1	17	**16·03**	±2·50	±0·60	**2·14**	1·98	P < 0·05*
	2	15	**16·00**	±1·34	±0·35	**2·20**	1·98	P < 0·05*

* Difference between ocular tension in emmetropic and myopic eyes significant

Discussion

The factors most likely to be responsible for differences in applanation readings are the thickness of the cornea, the volume of the eye, and the accommodation. Goldmann

(1957) reported that pliability of the cornea affected the force needed to flatten a given area, and that the extra force required was equal to that exerted by surface tension if the diameter of the applanation was 3·06 mm. Murata and Kato (1963) measured the thickness of different areas of the cornea, in emmetropia and ametropia, using a corneal pachometer, and found that the mean thickness in the centre of the cornea was 0·532, 0·487, and 0·536 mm. in emmetropic eyes, myopic eyes above −5 D sph., and hypermetropic eyes above +2 D sph., respectively. There was thus no significant difference between emmetropic and hypermetropic eyes, but a significant difference between emmetropic and myopic eyes. Shukla (1968) confirmed that the cornea is thinner in myopia than in emmetropia, and this probably applies to the sclera as well. Friedman (1966) showed that an eye of large volume with thin coats will experience greater stress on its coats than a normal eye at the same intraocular pressure. This greater stress means that more force is required in using the applanation tonometer, thus giving higher tension readings.

Friedenwald (1937) showed that variations in the radius of curvature of the cornea affected indentation tonometric readings, but Schmidt (1959) showed that such variations had very little effect on the results of applanation tonometry; the volumetric displacement in applanation tonometry of a cornea with a radius of curvature of 4·5 mm. was 0·995 cu. mm., while that of 15·5 mm. was 0·281 cu. mm. This very small difference in volume displacement between these extreme radii of curvature of the cornea could not be compared with the large volumetric displacement that occurs in indentation tonometry. Variations in the radius of curvature of cornea cannot therefore explain our results.

Friedenwald (1937), in calculating his formula for ocular rigidity, assumed that the volume of the eye is roughly constant. Phillips and Quick (1960) proved that the amount of indentation, apart from the other factors, is also dependent on the initial volume of the eye, and that eyes with different volumes but with equal internal pressure, would give different indentation tonometric readings. Friedman (1966) agreed with Phillips and Quick, but added that volume relationships in both applanation and indentation tonometric readings should be considered in calculating measurements of the intraocular pressure. He proved that eyes of different volumes have a different stress–strain relationship in all their coats, in spite of having the same intraocular pressure, so that this stress–strain relationship will affect tonometric readings whatever method is applied. Friedman concluded that in myopia there is no regular variation in ocular rigidity, but rather an average for each degree of refraction modified by age.

Sato, quoted by Becker and Gay (1959) in a monograph on myopia, demonstrated that the axial length of myopic eyes does not increase gradually and proportionately with the refractive error, but that there is a sharp increase between −2 and −5 D sph., after which the increase in the axial length is small but gradual. Toselli (1961), studying the course and evolution of myopia in the first three decades of life, found that myopia showed a progressive phase with quiescent intervals in 96·5 per cent. of myopes aged 2 to 20 years, only 3·5 per cent. remaining stationary, whereas in those aged 20 to 30 years the myopia remained stationary in 12 per cent. The work of Sato and of Toselli (1961) may explain the differences obtained in cases of moderate myopia in the second decade of life in our series; the marked growth of the eye changes its volume and perhaps the stress–strain characteristics of the cornea, so affecting the applanation tonometric readings.

Levene (1961), Draeger (1961), Fukuda (1961), Diaz-Dominguez (1961), and Armaly (1965) found that the intraocular pressure increased with age. The same result was found in our series, the increment being more pronounced and statistically significant in older myopes. The other likely explanation of the significant results obtained in our series in myopes above 40 years of age may be the different thickness of the ocular coats in myopia, which is also modified by changes in the volume and age.

Finally, the factor of accommodation should be considered in discussing the difference in applanation tonometric readings between myopes and emmetropes. Armaly and Burian (1958) and Armaly and Rubin (1961) found that eyes with powerful ciliary muscles have a lower intraocular pressure than those with weaker ciliary muscles when accommodation takes place during tonometry. It is possible that the difference in mean tension between the emmetropes and myopes in our series is partly due to this cause.

Conclusion

The results of a study of 760 subjects demonstrate a significant relationship between applanation pressure and errors of refraction, and indicate that the patient's age should also be taken into account.

The significant differences between emmetropes and myopes are due to biological variations related to the structure and thickness of the cornea, accommodation, and the volume of the eye.

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Estimation of sodium fusidate* levels in human serum, aqueous humour, and vitreous body

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The blood–aqueous barrier prevents, in the healthy eye, the passage of large molecules like those of ampicillin from reaching satisfactory therapeutic levels in the anterior chamber (Kurose, Levy, and Leopold, 1950). Systemic antibiotics are prescribed for patients suffering from intraocular sepsis in the belief that the antibiotic penetrates into the inflamed eye secreting a plasmoid aqueous with or without cellular elements. However, many such cases do not progress satisfactorily and it becomes incumbent on the ophthalmologist to demonstrate in the human aqueous effective therapeutic levels of antibiotics preferably with marked anti-staphylococcal activity.

The first two purposes of this study were (1) to devise a simple, safe technique for the removal of aqueous in human subjects, and (2) to estimate the level of sodium fusidate in aqueous and serum simultaneously. Sodium fusidate was chosen because of its marked action against *Staphylococcus pyogenes* both *in vitro* (Godtfredsen, Roholt, and Tybring, 1962; Barber and Waterworth, 1962; Hilson, 1962; McDonald, 1965; Harvey, Sih, and Knight, 1965), and *in vivo* (Scowen and Garrod, 1962; Taylor and Bloor, 1962; Cusack, 1962; Newman, Bhat, Hackney, Robinson, and Stewart, 1962; Thibault, 1962; Crosbie, 1963; Porter and Wilson, 1963; Jensen and Lassen, 1964; Healy, 1966; Saggers, Harwood, and Day, 1968).

Patients who have had several attacks of uveitis may come to surgery for cataract extraction. They may be regarded as in need of antibiotic cover.

The third purpose of this study (3) was to demonstrate the passage of sodium fusidate into the aqueous of patients who had suffered several attacks of iridocyclitis.

Methods

PHASE I

The nature of the study was explained to each of eighteen patients about to undergo routine cataract extraction under local anaesthesia. They were asked to take 500 mg. sodium fusidate three times a day for 3 days (6 patients), for 2 days (6 patients), or for 1 day (6 patients). The final dose of sodium fusidate was given 12 hours before surgery (Table I, opposite).

10 ml. blood for serum sodium fusidate estimation were withdrawn while the retrobulbar anaesthetic was taking effect. The eye was grasped at the insertion of the medial rectus. The tip of a

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*Fucidin, Leo Laboratories

Table I *Serum and aqueous levels of sodium fusidate in patients prepared for cataract extraction*

Patient no.	*Age (yrs)*	*Sex*	*Duration of fusidate therapy (days)*	*Sodium fusidate levels (μg./ml)*		*Comments*
				Serum	*Aqueous*	
1	74	M	3	52	1·28	
2	74	M	3	72	1·28	
3	68	M	3	58	1·2	
4	58	F	3	64	1·2	
5	65	M	3	70	1·28	
6	65	M	3	3·2	<0·16	Patient had not taken tablets as directed
7	62	F	2	64	0·8	
8	60	M	2	64	1·2	
9	58	M	2	40	1·2	
10	70	M	2	18	1·2	
11	58	F	2	64	1·2	
12	62	F	2	64	—	Aqueous sample inadequate
13	57	F	1	28	0·48	
14	64	F	1	36	0·84	
15	60	F	1	16	0·22	
16	70	M	1	32	0·24	
17	80	M	1	4	0·08	
18	74	F	1	23	0·10	

disposable needle (Yale 25 G 5/8 No. 18) connected to a 2 ml. disposable syringe containing 0·5 ml. air was inserted 0·25 mm. from the limbus through the cornea into the anterior chamber. In the case of a patient undergoing right cataract extraction, the needle was inserted at the "9 o'clock" position, and "3 o'clock" was the position for a left cataract extraction. The syringe was held horizontally throughout this procedure. At no time was any difficulty experienced in inserting the tip of the needle. The surgeon's assistant slowly withdrew two or three drops of aqueous and replaced the deficit with air from the syringe. There was no need to detach the syringe or withdraw the needle until the procedure was completed.

Routine cataract surgery was then performed. No difficulty in completing the operation was experienced in any case.

PHASE 2

Two patients with diabetes mellitus, recurrent iridocyclitis, and cataracts were given 500 mg. sodium fusidate three times a day for 3 days, and the cataracts were then removed.

Finally, in order to reduce the formation of aqueous and so reduce the intraocular pressure, carbonic anhydrase inhibitors may be prescribed in patients with intraocular sepsis complicated by glaucoma. The effect of this reduction of flow on the level of sodium fusidate in the aqueous has been investigated (4).

PHASE 3

Eight patients with high myopia were given Diamox 500 mg., and then 250 mg. 3-hrly for 24 hours before operation. 500 mg. Diamox was given intramuscularly on the morning of the operation. This is the standard procedure employed by one of us (J.W.) in such cases. Three of these patients received sodium fusidate 500 mg. three times a day for 3 days, two for 2 days, and three for one day (Table II, overleaf).

Table II *Serum and aqueous levels of sodium fusidate in cataract patients treated with sodium fusidate and Diamox*

Patient no.	*Age (yrs)*	*Sex*	*Duration of fusidate therapy (days)*	*Sodium fusidate levels (μg/ml.)*	
				Serum	*Aqueous*
1	70	M	3	70	1·34
2	72	F	3	96	2·56
3	68	F	3	68	1·32
4	59	F	2	40	1·2
5	60	M	2	28	0·84
6	60	M	1	8	0·16
7	61	F	1	24	0·42
8	63	F	1	4	0·03

PHASE 4

During a 6-month period three patients presented with blind painful eyes (Table III).

The first two received 500 mg. sodium fusidate four times a day for 4 days; 12 hours after the last dose the eye was enucleated, and aqueous was removed through the centre of the cornea, and vitreous *via* a small stab wound in the sclera.

The third patient received the same amount of sodium fusidate as the other patients, but the eye was not removed until 4 days after the last dose of Fucidin. Serum, aqueous, and vitreous samples were taken on the day of the operation.

Table III *Levels of sodium fusidate in serum, aqueous, and vitreous*

Patient no.	*Age (yrs)*	*Sex*	*Duration of fusidate therapy (days)*	*Sodium fusidate levels (μg./ml.)*		
				Serum	*Aqueous*	*Vitreous*
1	58*	F	3	84	12·8	28·8
2	60	M	3	56	>0·64	>0·64
3	56†	F	3	0·9	0·1	0·32

* Aqueous and vitreous levels excessively high, probably due to increase in protein content associated with prolonged inflammation
† Last dose of Fucidin 4 days before enucleation.

Laboratory technique

Sodium fusidate was assayed by an agar plate diffusion technique using *Corynebacterium xerosis* as test organism. The method was that used by Leo Laboratories Ltd.

Two strains of the test organism, Leo strains FF and FF(M), were sodium fusidate sensitive; strain FF was used constantly. Another strain, FF (ZN6), was sodium fusidate resistant, and was used to detect the presence of other inhibiting agents, either in the material under test, or in the pooled serum used as diluent in the serum and vitreous assays (the assay medium was employed also as a maintenance medium in the form of slopes).

The phosphate buffer used to prepare the standard dilution was adjusted to pH 6·3 since this increased the sensitivity of the assay.

AQUEOUS ASSAY

Holes 6 mm. in diameter were made in the agar and 1 drop of standard or test dilution was placed in each. The standards for this assay were 0·32, 0·16, 0·08, 0·04, and 0·02 μg/ml., measurable inhibition was constantly observed with 0·04 μg/ml. Aqueous humour was usually diluted 1 in 4 with buffer (1 in 8 if quantity permitted).

Zone diameters of inhibition were measured, and the results transferred to a simple graph of concentration (μg./ml.) against zone diameter of inhibition (mm.), and the aqueous concentration was thus measured. Since an initial dilution of aqueous humour was generally made, the minimum detectable amount of antibiotic in aqueous was usually 0·16 μg./ml.

SERUM AND VITREOUS ASSAY

Standard solutions (6·4, 3·2, 1·6, 0·8, and 0·4 μg./ml.) of sodium fusidate were prepared in pooled human serum. Aliquots were then diluted with three volumes of phosphate buffer. The test serum was usually diluted 1 in 10, and 1 in 20 with pooled serum, and then aliquots were further diluted with three volumes of buffer.

Results

The results of Phase 1 are shown in Table I. As expected, the serum levels of sodium fusidate rose steadily as patients received 1, 2, or 3 days of the antibiotic (1 day mean 23·3 μg./ml., 2 days mean 52·3 μg./ml., 3 days 63·2 μg./ml.). The aqueous levels behaved a little differently in that after only 48 hours adequate therapeutic amounts of sodium fusidate had penetrated into the aqueous (1 day mean 0·33 μg./ml., 2 days mean 1·12 μg./ml., 3 days mean 1·25 μg./ml.).

There was no impediment to the passage of sodium fusidate into the aqueous in the two diabetic patients who had had recurrent bouts of iridocyclitis. Serum levels were 70 and 58 μg./ml. and the aqueous levels 1·32 and 1·2 μg./ml. respectively.

To our surprise, the carbonic anhydrase inhibitor, Diamox, did not reduce the level of aqueous sodium fusidate (Table II). Indeed, some of the highest aqueous levels were obtained in this group of patients, *e.g.* 2·56 and 1·34 μg./ml. However, the overall levels were not significantly higher than in the group of patients who did not receive Diamox.

Sodium fusidate was detected in the vitreous of three patients (Table III). In two cases the vitreous level was between two and three times as high as in the aqueous, and a fairly high vitreous level of sodium fusidate was still present 4 days after the last dose of the drug in one patient.

Discussion

48 hours' treatment with 500 mg. sodium fusidate three times a day produced adequate aqueous levels. It is suggested that the clinician might look for beneficial results from sodium fusidate therapy after 2 days, and that 2 days of therapy should give adequate prophylactic cover.

Since Diamox did not inhibit the penetration of the antibiotic into the aqueous humour, it would appear that sodium fusidate diffuses through the blood–aqueous barrier, requiring no active transportation across the ciliary body epithelium.

Only two patients with a history of repeated attacks of iridocyclitis were included in this survey. In neither did the antibiotic fail to penetrate into the aqueous. However, a larger series should be studied before any conclusions are drawn.

The vitreous levels of sodium fusidate were two to three times as high as the aqueous levels in two patients; 0·32 μg./ml. was found in one patient's vitreous 4 days after the drug had been discontinued. In addition to the same proteins as are found in the aqueous, the vitreous contains vitrein and mucoid (Adler, 1959). The vitreous, therefore, has a higher protein-binding capacity than the aqueous though not as high as that of serum. This, in all probability, is the reason why sodium fusidate levels are higher in the vitreous than in the aqueous.

Summary

Sodium fusidate (Fucidin, Leo Laboratories) was demonstrated in the aqueous humour of 25 human patients about to undergo cataract extraction and in three patients requiring enucleation. Adequate therapeutic levels were detected in all the patients who were given either 2 or 3 days' therapy. Neither previous iridocyclitis nor carbonic anhydrase inhibition prevented the passage of the antibiotic into the aqueous. The sodium fusidate had penetrated into the vitreous body of the eyes that had to be enucleated and because of the higher protein-binding capacity of the vitreous the levels of antibiotic were higher there than in the aqueous humour.

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Dermoid cyst of great wing of sphenoid bone

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Hartmann and Gilles (1959), Reese (1963), and Duke-Elder (1964) have described the *x*-ray picture of deep orbital dermoid cysts, stressing the importance of their exact localization for proper surgical treatment. Among nine cases reported by Pfeiffer and Nicholl (1948) there were seven affecting the frontal bone, and two the lateral wall of the orbit or great wing of the sphenoid bone.

The following case is described because such cysts very rarely affect the diploic bone of the great wing of the sphenoid bone.

Case report

A 16-year-old girl (Fig. 1) had right downwards and inwards proptosis of 20 mm. (left side 16 mm. Hyrtel) of 10 months' duration. There was no ocular pain and no limitation of ocular movements. The right and left fundi were normal, and the visual acuity 6/12. There was no external palpable orbital mass. The general condition of the patient was good.

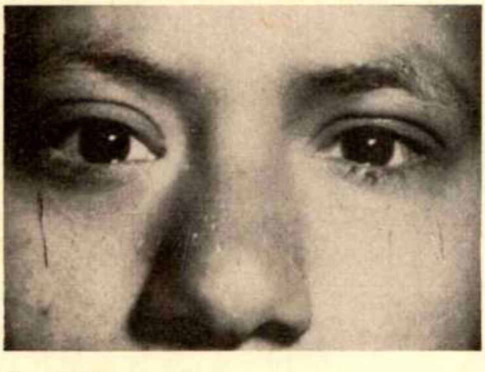

FIG. 1 *Case 1. Right proptosis due to dermoid cyst in diploic bones of right great wing of sphenoid bone of* 10 *months' duration in a girl aged* 16 *years*

Examination

Postero-anterior (Fig. 2), lateral, and oblique (Fig. 3) skull *x* rays (overleaf) showed widening of the right orbit and an area of loss of substance with a dense smooth sharply-defined margin affecting the right great wing of the sphenoid bone, thus suggesting a dermoid cyst. Both optic foramina were of normal dimensions.

Deep orbital palpation with the little finger through an external canthotomy incision showed that the bony reaction was due to extensions of the dermoid cyst into the diploic bones with irregularity and thickening of the great wing of the sphenoid bone.

Treatment

As removal of the great wing of the sphenoid bone with the contained dermoid cyst would endanger the brain in the middle cranial fossa the following treatment was adopted in accordance with the advice of Pfeiffer and Nicholl (1948). Through a lateral orbitotomy the cyst was incised and evacuated. Its inner wall was swabbed with carbolic acid and immediately neutralized by alcohol and irrigated by saline solution. The cyst wall was then removed as completely as possible.

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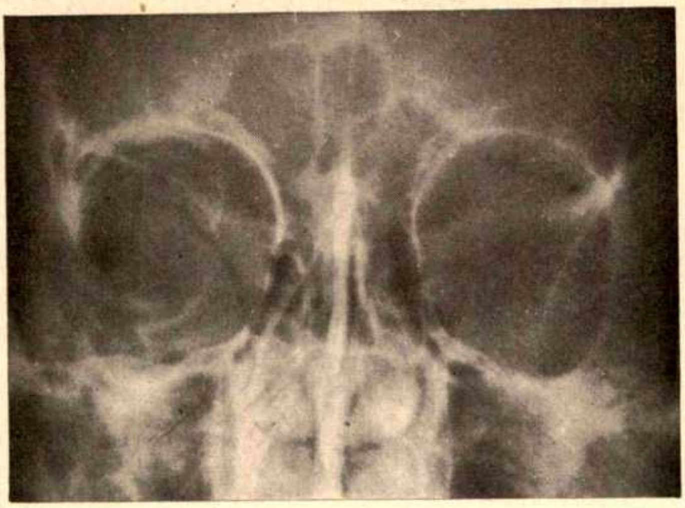

FIG. 2 *Case* 1. *Postero-anterior skull* X-*ray, showing loss of substance with a demarcated sclerosed margin due to dermoid cyst of right great wing of sphenoid bone*

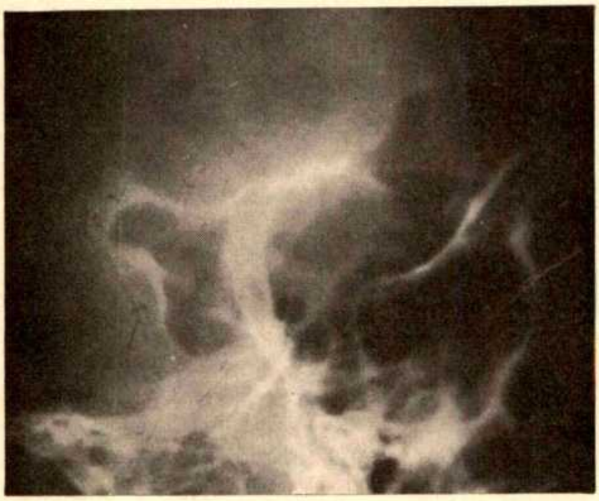

FIG. 3 *Case* 1. *Right oblique skull* X-*ray, showing loss of substance with sharply-defined margin due to dermoid cyst of right great wing of sphenoid bone*

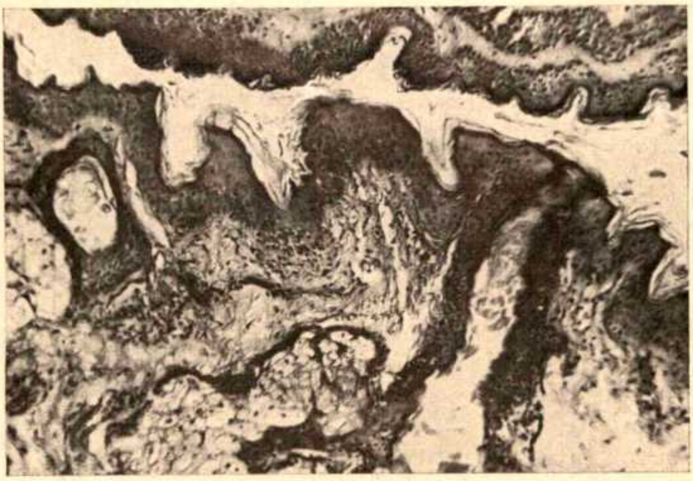

FIG. 4 *Case* 1. *Dermoid cyst of right great wing of sphenoid bone, showing epidermis and dermis containing sweat and sebaceous glands and hair follicles.* ×120

Histopathology

The cyst wall showed epidermis and dermis containing sweat and sebaceous glands and hair follicles (Fig. 4). The cyst contained a brownish semi-fluid and hairs.

Summary

A deep orbital dermoid cyst affecting the diploë of the right great wing of the sphenoid bone caused proptosis in a 16-year-old girl.

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Brit. J. Ophthal. (1970) **54,** 134

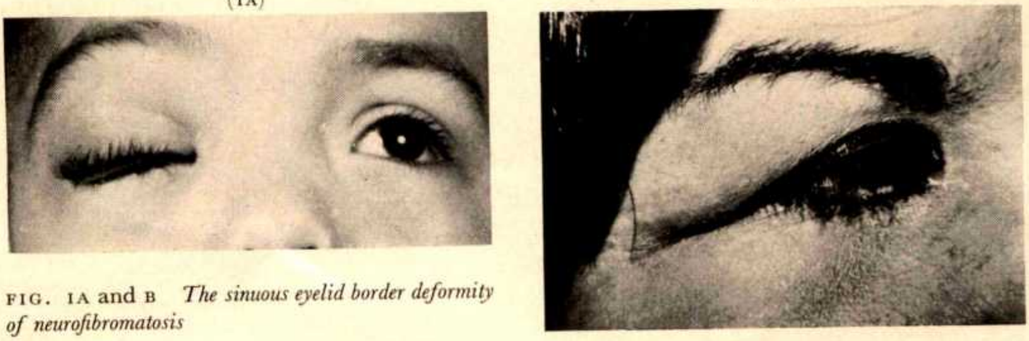
Classical eyelid border sign of neurofibromatosis

BYRON SMITH AND FRANK P. ENGLISH

From the Department of Ophthalmic Plastic Surgery, Manhattan Eye, Ear and Throat Hospital, New York

Neurofibromatosis is a well-documented entity, having been first recorded by von Recklinghausen (1882). When involvement of the orbit and eyelid occurs in this disease, the presentation may be manifold. Blepharoptosis commonly occurs and may be variable in degree. Where elephantiasis neuromatosa occurs in association with this, the drooping eyelid characteristically has the sensation of a bag of worms when palpated. In addition exophthalmos may or may not be present. Sometimes, where orbital bony defects exist, the globe has a pulsatile character; bone hypertrophy, however, may be the rule rather than bone destruction. The typical ocular and systemic manifestations of neurofibromatosis can also be associated with involvement of the orbit and these are well described in the literature (Reese, 1963).

Attention is drawn here to an important physical sign in the eyelid which is diagnostic of neurofibromatosis of the orbit. In this condition the lid margin of the ptotic eyelid displays a peculiar sinuous configuration, the lid border possessing an inner portion which arches upwards whereas the outer half assumes a downwards convexity (Fig. 1A and B).



(1A)

(1B)

FIG. 1A and B *The sinuous eyelid border deformity of neurofibromatosis*

In considering the aetiology of this physical sign, a number of factors must be considered. The site of the tumour is important. Surgical exposure demonstrates the bulk of the tumour to be located predominantly lateral to the belly of the levator palpebrae superioris muscle; this accounts for the accentuation of the lid margin temporally. The tumour lies in close proximity to the conjunctiva and hence the transconjunctival route represents the proper surgical approach to these lesions. Attempts at removal *via* the skin are usually doomed to failure and the tumour is neither identified nor removed. The septum orbitale does not appear to play a role in this deformity, and may even exert a restraining influence as the septum is best developed in its lateral portion.

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Address for reprints: F. P. English, F.R.C.S., Manhattan Eye, Ear and Throat Hospital, Clinic for Reconstructive Plastic Surgery of the Face, 210 East 64th Street, New York 21, N.Y., U.S.A.

Other important considerations include tarsal and integumental features. In neurofibromatosis the tarsal plate is abnormally pliable and loses its supportive role. This softening of the tarsal plate results in its distortion by movements of the eye. The same feature is sometimes seen in well-established trachoma (Herbert, 1907), when a similar change has occurred in the tarsal plate. The skin in neurofibromatosis is characterized by hyper-elasticity and can often be greatly stretched depending on the degree of involvement (Fig. 2); this loss of support is also partly responsible for the shape of the eyelid.

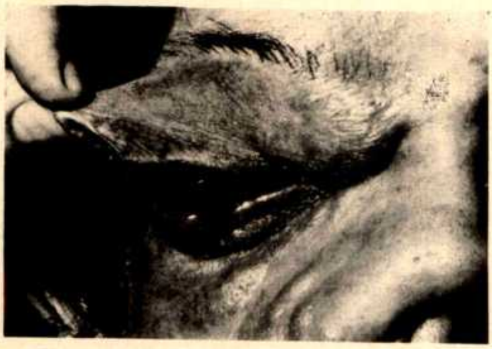

FIG. 2 *Characteristic hyper-elasticity of the skin in neurofibromatosis*

In the differential diagnosis, trachoma must be considered, as on rare occasions in advanced cases it can produce a similar clinical picture, but this is not as marked as in neurofibromatosis.

Summary

In neurofibromatosis of the orbit and eyelids, a sinuous deformity of the border of the eyelid is a common finding and is diagnostic of the condition.

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Brit. J. Ophthal. (1970) **54**, 136

Posterior lenticonus with involvement of foetal nucleus

DALJIT SINGH AND DHANWANT SINGH

Department of Ophthalmology, Government Medical College, Patiala, India

Posterior lenticonus is a prominent spheroid elevation occurring on the posterior surface of the lens. Since the first case was observed by Meyer (1888: see Duke-Elder, 1964), some hundred cases have been reported. The condition is usually complicated by the presence of posterior polar lens opacities, which may be dust-like, trumpet-shaped, rosette-like, or in reduplicated forms resembling a collar-stud. These disturbances have been seen to involve only the outer zones of discontinuity, without disturbing the foetal or embryonal nucleus. A case of posterior lenticonus is reported below, in which a tube-shaped opacity extended from the globus area into the lens and involved the posterior half of the foetal nucleus.

Case report

A 13-year-old girl came to the clinic with the complaint of poor vision in the right eye since birth. Before the pupil was dilated, a posterior lenticular opacity with a curious dark circular area could be seen. After dilatation ophthalmoscopic examination revealed the typical circular ring reflex of posterior lenticonus. Slit-lamp examination showed the lenticonus to be limited to about 1·5 mm. diameter in the middle of the posterior surface of the lens. A white tube-shaped opacity of granular texture was found to extend from the area of lenticonus into the substance of the lens for a considerable distance (2·5 to 3 mm.). The cavity of the tube appeared to be empty. The outer end of the tube was opaque as were the sides.

Optical section revealed that, whereas the anterior Y-suture was plainly visible, the posterior ⅄-suture could not be found, nor could we find the posterior part of the foetal nucleus, the place of both these structures being occupied by the empty space inside the tube-shaped opacity. Remnants of the hyaloid vessels could be faintly seen on the back of the globe. The Figure shows details of the lenticonus and opacity in section. The anterior end of the opacity was expanded. The circular reflex was caused by the zone of specular reflection at the place where the capsule makes a sudden turn in the frontal plane.

Retroillumination showed that the disturbance in the lens was even more extensive, being about four times the area of the lenticonus. This abnormal area was sharply delineated from the normal lens substance. Just below and lateral to the lenticonus the capsule had the appearance of crocodile skin, and beside it was a sickle-shaped area of a uniform dark appearance.

The corrected visual acuity was 5/60, with +1·5 D sph., and there was a divergent squint of 15°.

Comment

The causation of lenticonus is a matter of controversy. The widespread disturbances in the lens and lens capsule beyond the area of the lenticonus in this case suggest that the malformation was due to the herniation of lens substance through a weakened capsule.

Received for publication June 10, 1969
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Full information is available on request

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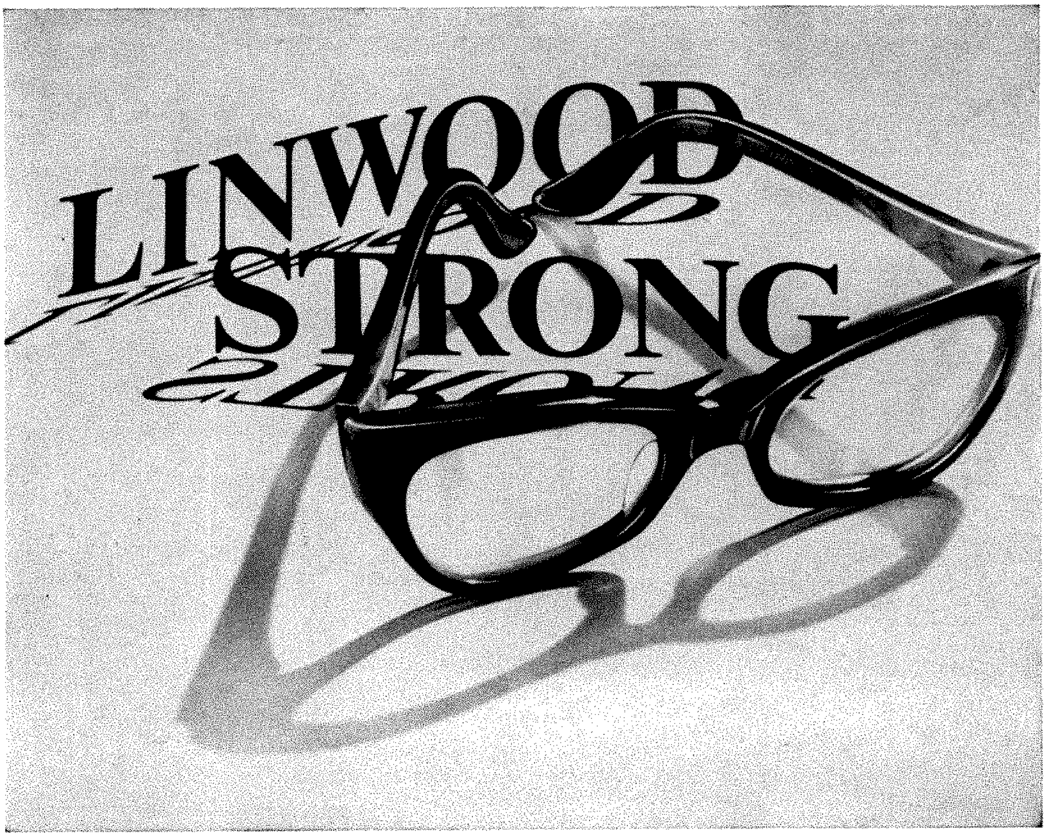

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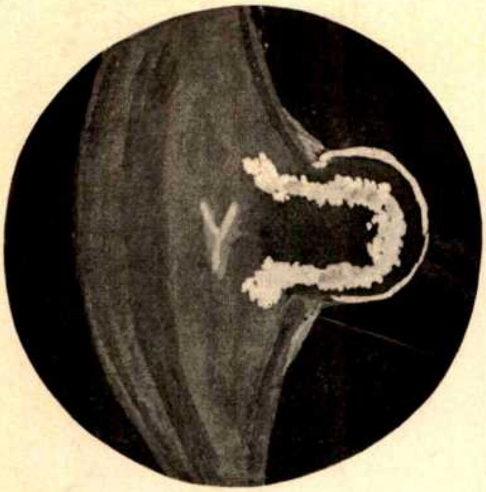

FIGURE *Optical section, showing anterior Y-suture and tube-like opacity*

Summary

A case is reported of posterior lenticonus with a tube-like opacity running from the dorsal bulge anteriorly, enclosing an optically empty space and involving the posterior λ-suture and foetal nucleus.

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Brit. J. Ophthal. (1970) **54**, 138

Fascia lata rack for retinal detachment surgery

P. N. HENDERSON, J.-M. PAREL, AND G. W. CROCK

From the Melbourne University Department of Ophthalmology, the Ophthalmic Research Institute of Australia, and the Royal Victorian Eye and Ear Hospital, Melbourne

The use of biological polymers for external plombage in retinal detachment surgery is well established (Havener and Wachtel, 1964; Klöti, 1964; Crock and Galbraith, 1966). Fascia lata is the tissue most widely employed because it is readily obtainable and is easily sterilized and stored (Havener and Olson, 1962). When tightly twisted it makes an ideal encircling element for scleral buckling.

This paper describes an instrument which facilitates the production of firm uniform cords from strips of fascia lata.

Instrumentation (Fig. 1)

The rack consists of a pair of toothed clamps mounted on vertical columns. When in use it is screwed perpendicular to the base (Fig. 2). Torque is applied to the fascia by a clamp which can be rotated about the horizontal axis and locked in any desired position. The twisted tissue is pulled taut by sliding one of the columns along a horizontal bar. This sliding system permits the distance between clamps to be varied from 50 to 170 mm. It can be locked anywhere within this range.

The base of the instrument is a shallow open box, inside which the rack is screwed for storage and sterilization (Fig. 3).

Technique

A strip of autogenous or irradiated cadaver fascia lata is trimmed to the desired width and folded on its long axis. The two ends are then clamped, and twisting and straining is applied until the desired cord diameter is attained. The instrument is locked and the central portion of the cord, which will be used to produce a scleral buckle, is stabilized by a running 5–0 plain cat-gut suture. The suture is inserted with a straight needle in the form of a key-hole stitch which is doubled back on itself in a plane at right angles to the first run. Interrupted stitches are then placed at 1 cm. intervals along the sutured cord (Fig. 4, overleaf).

After the scleral buckling procedure has been effected, the fascia lata at each end of the cord is untwisted, thinned by scalpel or scissors, and passed around the globe as an encircling element (Fig. 5, overleaf).

Discussion

Cryopexy and full-thickness scleral buckling for the repair of retinal detachment is now the standard procedure at the University of Melbourne Department of Ophthalmology. Scleral buckling is produced by tying mattress sutures over a twisted cord of fascia lata.

The instrument described was designed to enable an assistant to prepare a suitable cord of fascia while the surgeon prepares the eye for cryopexy and buckling. The cord so produced is firmer and more uniform than one fashioned manually.

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Address for reprints: P. N. Henderson, Melbourne University Department of Ophthalmology, 148 Victoria Parade, Melbourne, 3002, Victoria, Australia

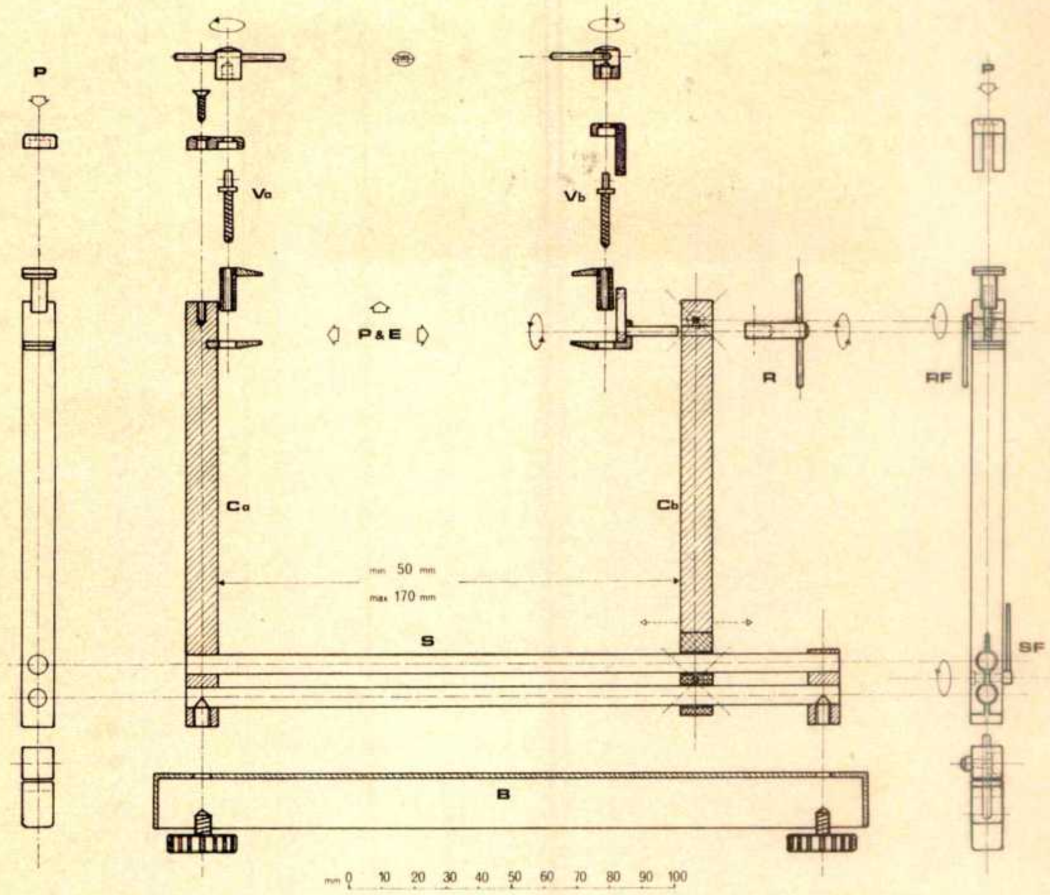

FIG. 1. *Design drawing of fascia lata rack*

P	projection;
B	base;
Ca	fixed column;
Cb	sliding column;
S	horizontal bars permitting adjustment of distance between clamps (range 50 to 170 mm.);
SF	sliding column lock;
Va	fixed fascia clamp;
Vb	rotatable fascia clamp;
R	rotating levers;
RF	rotatable clamp lock

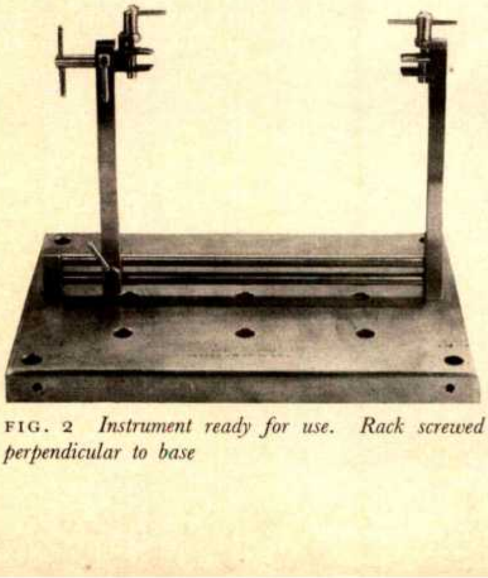

FIG. 2 *Instrument ready for use. Rack screwed perpendicular to base*

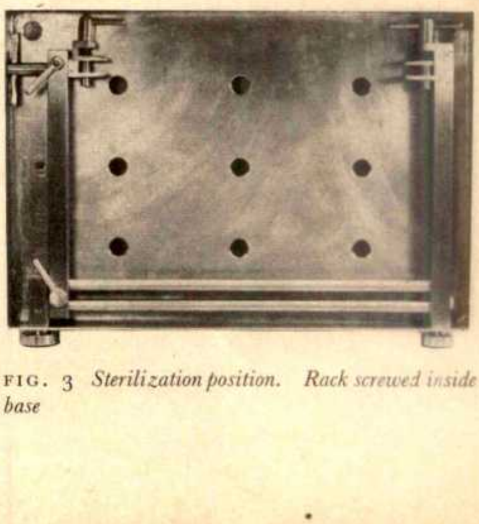

FIG. 3 *Sterilization position. Rack screwed inside base*

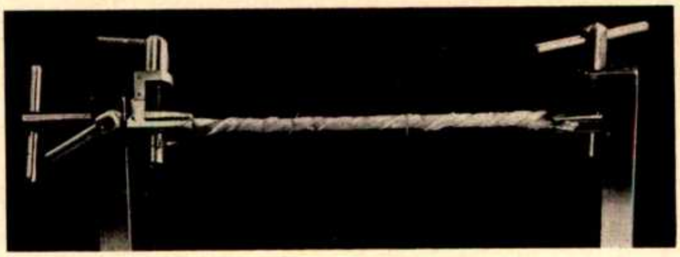

FIG. 4 *Twisted fascia lata cord sutured in central portion with continuous and interrupted 5–0 catgut stitches*

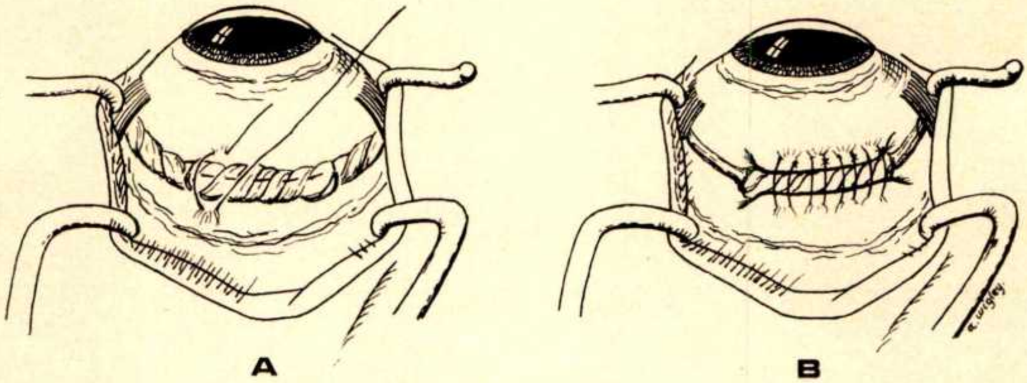

FIG. 5. *Twisted fascia lata cord in use*

A. Scleral buckling with 5–0 braided dacron mattress sutures

B. After scleral buckling the fascia at each end of the cord is thinned and passed around the globe as an encircling element

Summary

An instrument is described which twists fascia lata into a cord for encircling plombage in retinal detachment surgery. The implant, which can be produced rapidly without assistance, is firmer and more uniform than one fashioned manually.

The instrument was made from corrosion resisting steel by L. Pericic. Mr. A. Wigley and Mrs. G. Van den Brenk were responsible for the illustrations.

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Book reviews

Corneo-Plastic Surgery (Proceedings of the Second International Corneo-Plastic Conference). Edited by P. V. RYCROFT. 1969. Pp. 628, numerous figs, bibl. Pergamon Press, London. (£10.)

The late Benjamin Rycroft arranged this gathering of the world's experts in the fields of corneal and plastic surgery, and the papers there presented and the discussions that followed are contained in this beautifully produced volume. The standard of production of the book is first class throughout and the articles are profusely illustrated with pictures of great clarity. Such a volume is not intended to be comprehensive but the papers are so varied in their context that every aspect of the subject is included.

Ptosis and lid reconstruction are treated at length. Modern approaches to lacrimal and orbital surgery are also well covered. Every aspect of keratoplasty from the biological and immunological to the details of many specific surgical procedures are discussed. There are sections, too, relating to ophthalmic pathology and bacteriology, the applications of contact lenses, and the surgery of the iris and ciliary body. Opinions and experiences of experts in their fields from over 42 countries will be found.

Although the book deals with a specialized aspect of ophthalmic surgery, much will be found of interest and of real value to every ophthalmic practitioner.

Recommendations for the Treatment of Ocular Diseases (Therapeutische Empfehlungen zur Behandlung von Augenkrankheiten). By V. KITTEL. 2nd ed., 1969. Pp. 118 (*Abhandl. Augenheilk.*, 31). Thieme, Leipzig. (*DM* 14.20).

The first edition of these recommendations, intended by the author as a short reference book for the budding ophthalmologist during and after his years of training, has found so many enthusiasts, presumably among his not so very young colleagues, that a second edition has become necessary. While it is intended not to overstep the self-imposed limits of a short guide to everyday ophthalmic therapy, certain newer methods which have recently been developed and have gained a firm foothold in the specialty have been included at the expense of some older, now rarely-adopted procedures. This applies in the first place to the use of corticosteroids in uveal diseases, for which a neat scheme has been elaborated for use in cooperation with the medical specialist. Other interesting schemes concern the use of anticoagulants and of fibrinolytics in retinal arterial and venous thromboses with, no doubt, the intention of combating the attitude of therapeutic nihilism mostly adopted towards these diseases. However, we are not told how effective all this is. A detailed description of the drugs used in ophthalmology is appended; this is a very useful reference list, provided the specifics current in Germany can be translated into their equivalents accessible to the reader.

Ocular Circulation in Health and Disease (William Mackenzie Centenary Symposium). Edited by J. S. CANT. 1969. Pp. 270, figs, bibl. Kimpton, London. (65*s*.)

The main value of specialized symposia lies in the meeting of a large number of people interested in the same basic subject, and the success of this present Conference was reflected in the detailed discussions which followed the formal communications. These papers are here published under four main headings: (1) Anatomy and Physiology of the Ocular Circulation; (2) Techniques of Investigation; (3) Systemic Vascular Disease; (4) Vascular Retinopathies.

The contributions to each of these sections reflect the active work that is going on in these subjects by a wide variety of investigators.

Prof. David Cogan gave the William Mackenzie Memorial Lecture on "Retinal and Papillary Vasculitis".

The book as a whole forms a most useful compendium for academic and clinical ophthalmologists interested in the ocular circulation in health and disease.

Fluorescein Angiography of the Retina. Textbook and Atlas. By A. WESSING. Trans. G. K. VON NOORDEN. 1969. Pp. 222, 120 figs, bibl. Mosby, St. Louis; Kimpton, London. (207*s.*)

The interest aroused by the publication of Wessing's original German textbook and atlas in 1968 has led to its translation into English by G. von Noorden. That it is highly recommended is evident from our previous review: *Brit. J. Ophthal.* (1968), **52**, 429.

New and Controversial Aspects of Retinal Detachment. Edited by A. McPHERSON. 1968. Pp. 509, 378 figs, refs. Harper and Row, London. (£7).

These are the proceedings of the symposium on retinal detachment held at Houston, Texas, in 1965.

The first section is concerned with the fine structure of the vitreous and retina and with the pathology of peripheral retinal degenerations. The second, and main, section is concerned with the management of detachments, and contains interesting and informative papers on methods of examination, coagulation techniques, scleral buckling, intraocular injection, and functional results. The short third section is on complications of surgery.

This is an excellent series of papers on a wide range of subjects pertaining to retinal detachment. The authors are acknowledged authorities on their subjects and much can be learned from reading these papers. This book can be thoroughly recommended.

Advances in Ophthalmology. Vol. 21. Edited by M. J. ROPER-HALL, H. SAUTTER, and E. B. STREIF. 1969. Pp. 236, 48 figs, refs. Karger, Basel. (Suppl. 80 to *Bibliotheca Ophthalmologica*). (SFr/DM 69; £6 18*s.*)

This volume follows the policy of this series to publish as monographs extensive reviews or original papers too long for inclusion in the conventional ophthalmic journals. The original works discuss local therapy in herpetic keratitis and the intraocular penetration of steroids. The reviews deal with non-magnetic intraocular foreign bodies, fluorescein fundus photography, vertebro-basilar vascular disease, and lens metabolism; they are exhaustive and non-critical. There is also a review *cum* original paper on electrodiagnostic tests in diseases of the posterior pole.

Operative Surgery. Vol. 10. Eyes and Ear, Nose and Throat. Edited by C. ROB and R. SMITH (Consultant editors: S. DUKE-ELDER and M. ELLIS). 1969. Pp. 340, figs, refs. Butterworth, London. (£8).

There is a commonly-held belief that, if one assembles a group of experts to write succinctly on their specialty, the combination of their works will be the best available text on the subject. This volume goes a long way to disprove this belief. In 90 pages seven experts have presented a clearly written and well-illustrated guide to ophthalmic surgery, but in such a short space much has been left out and there is no place for discussion of controversial aspects. The inclusion of lasers may support the claim that the volume is up to date, but there is no mention of microsurgery. The ophthalmic section is partnered by a longer section on ear, nose, and throat surgery: one wonders who will be inclined to buy such a book. As it is part of a multivolumed treatise, no doubt designed to present all that is best in British surgery, it may be that the ophthalmic section stands on equal footing with the rest. This places a considerable burden of selection on the overall editors, which seems not to have been shouldered in the present volume as the operation of dacryocystorhinostomy is described twice.

Amotio Retinae. Contributions to the Pathogenesis and Treatment of Retinal Detachment. (Amotio retinae. Beiträge zur Pathogenese und Therapie der Netzhautablosung). Edited by W. Doden. 1970. Pp. 135, 80 figs (Bücherei des Augenarztes, No. 53). Enke, Stuttgart. (DM 26).

This booklet contains the papers and lectures on retinal detachment which were read at an ophthalmological meeting at Frankfurt am Main in November, 1968. Thirteen well-known authors contributed. Custodis discussed scleral plugs and globe-shortening operations. Meyer-Schwickerath, of light-coagulation fame, gave a survey of detachment treatment. Hruby contributed a paper on the substitution of vitreous; recommending Etamucin, a hyaluronate. Other chapters deal with cryopexy, laser coagulation, half-*cerclage*, and the significance of changes of the vitreoretinal layer. Klöti stated in a very instructive way that a chorio-retinal defect was responsible for the tear while the vitreo-retinal relationship determined the shape and extent of the detachment. Hommer pointed out that the general reduction of the electroretinogram had no great diagnostic significance. When the media were cloudy the echogram gave more reliable results.

The booklet contains much valuable information, and gives a clear picture of today's views on retinal separation. One misses, however, the lively exchange of opinions which made the reading of the analogous reports of the Retina Foundation, Boston, 1965, so interesting.

Notes

Pediatric Ophthalmology Course

University of Toronto, April 2 to 4, 1970

The Department of Ophthalmology of the University of Toronto announces a University sponsored course in Pediatric Ophthalmology to be held on April 2, 3, and 4, 1970, in the Large Lecture Theatre, at the Hospital for Sick Children in Toronto, Ontario, Canada.

Guests of honour will be Mr. Kenneth Wybar, Chief of Ophthalmology at Great Ormond Street Hospital for Sick Children, London, England; Dr. Harold G. Scheie, Professor of Ophthalmology at the University of Pennsylvania, Philadelphia; and Dr. Hermann Burian, Professor of Ophthalmology at the University of Iowa, Iowa City, U.S.A.

IV Asia-Pacific Congress, 1972

Auckland, April 9 to 14, 1972

The Asia-Pacific Academy of Ophthalmology will hold its Fourth Congress at Auckland, New Zealand, on April 9 to 14, 1972. Distinguished speakers will discuss the surgery of glaucoma, cataract, and retinal detachment. Special consideration will be given to ophthalmic problems arising in the Asia-Pacific area. Scientific and trade exhibitions will be included.

The Committee extends a cordial invitation to all ophthalmologists to attend this Congress. Further particulars may be obtained from Dr. G. Fenwick, 17 Mount Street, Auckland 1, or from Dr. W. J. Holmes, 1013 Bishop Street, Honolulu, Hawaii.

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Obituary

Hans Reiter, 1881–1969

Our readers will regret to learn of the death on November 25, 1969, of Hans Reiter, one of the greatest bacteriologists and hygienists of our time. Born in Leipzig, he studied widely, spending 2 years in St. Mary's Hospital in London under Sir Almroth Wright. He was professor of hygiene at Rostock and then went to Berlin where he worked under Wassermann at the Kaiser Wilhelm Institute of Experimental Therapy. A dignified and courteous figure, he will be remembered for the isolation of the organism causing Weil's disease, for the elaboration of the Reiter complement-fixation test for syphilis, and particularly for the assessment of the syndrome of Reiter's diesase, with its triad of urethritis, arthritis, and conjunctivitis.

John Stanley Arkle (1890–1969)

John Stanley Arkle died suddenly on November 19, 1969, in his eightieth year. He was born in Newcastle upon Tyne on July 28, 1890, and after a short spell of studying to become an actuary decided to make his career in Medicine. At Durham University Medical School in Newcastle upon Tyne he was a brilliant undergraduate; he won many prizes, was awarded a gold medal, and graduated M.B., B.S. with honours in 1913. He served with the R.A.M.C. throughout the first world war and was awarded the O.B.E. in 1919 for his valuable services. After the war he studied at Moorfields Eye Hospital and later at Edinburgh where he took the F.R.C.S.E. in ophthalmology in 1920. In 1949 he was elected to the F.R.C.S. England *ad eundem.*

He was appointed honorary assistant ophthalmic surgeon to the Royal Victoria Infirmary, Newcastle upon Tyne, in 1920 and in 1928 became full surgeon and head of the department and also lecturer in ophthalmology at Durham University. For some years he was also honorary ophthalmic surgeon to Durham County Hospital and the Fleming Memorial Hospital for Sick Children. A regular attender at ophthalmological meetings and congresses, he was President of the North of England Ophthalmological Society in 1949 and of the Section of Ophthalmology at the British Medical Association annual meeting in 1957.

Stanley Arkle will long be remembered by all who knew him—fellow consultants, students, general practitioners, and patients —for his kindliness, forthright honesty, and helpful advice. He was an extremely modest man and went out of his way to help others in an unobtrusive manner.

He retired from the posts of Departmental head and Lecturer in 1950, five years before he was due to do so because he felt this would help his juniors who had been absent during the war years. Nevertheless, such was his greatness that he continued to serve the hospital as Associate Surgeon until his final retirement in 1955.

His wife died in 1955, but he is survived by his son and daughter both of whom are doctors.

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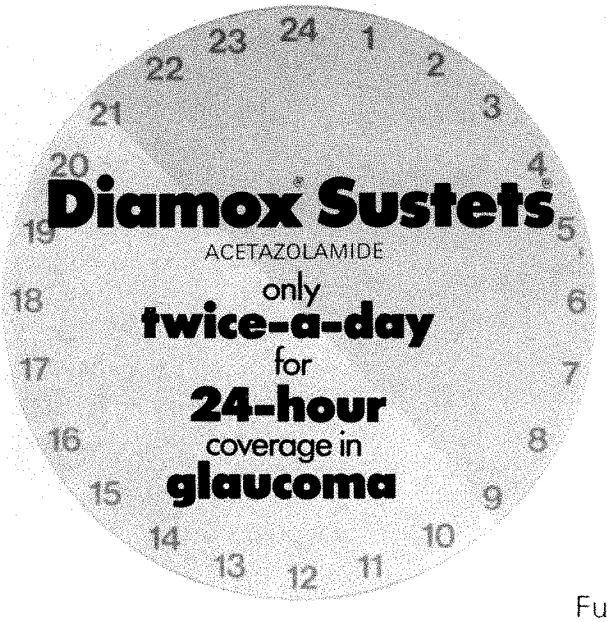

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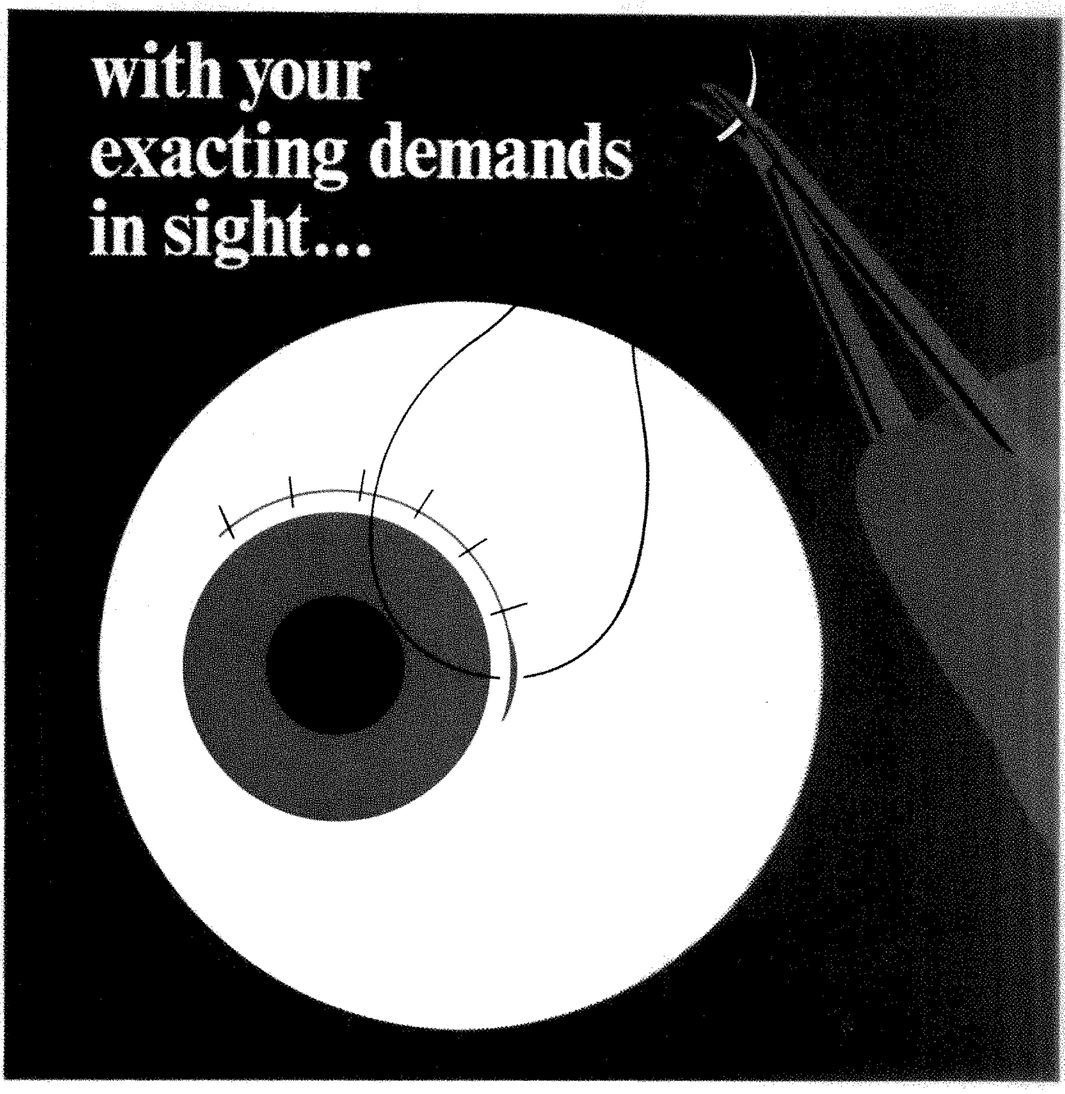

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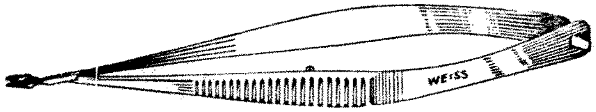

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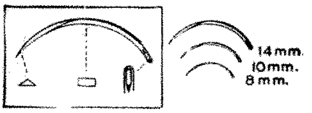

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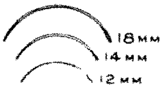

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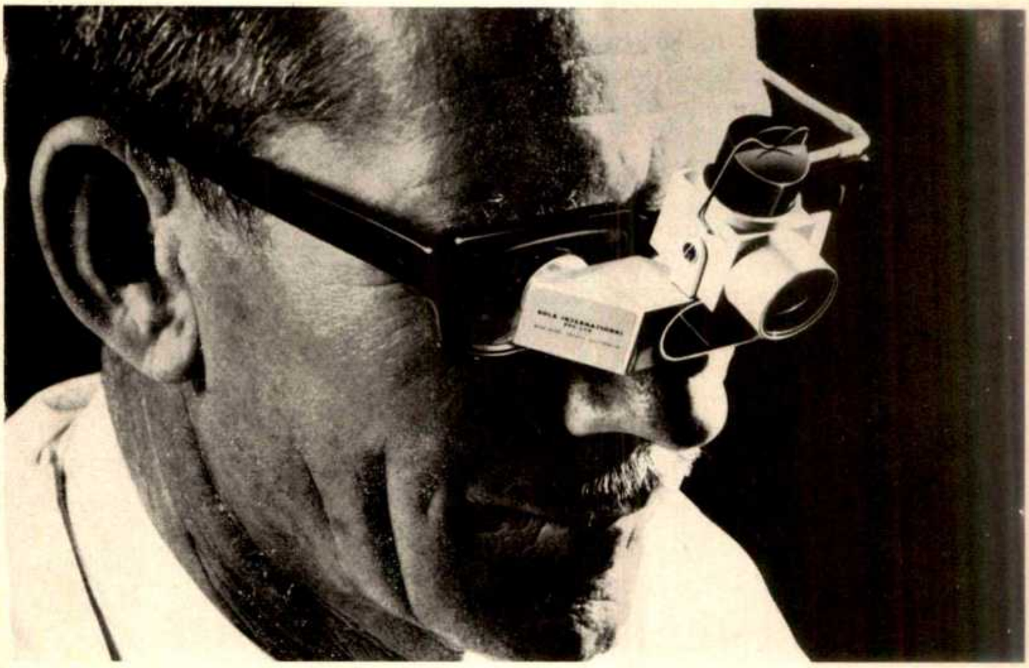

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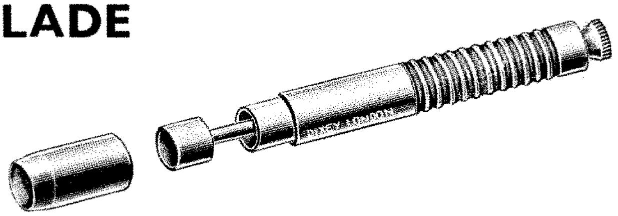

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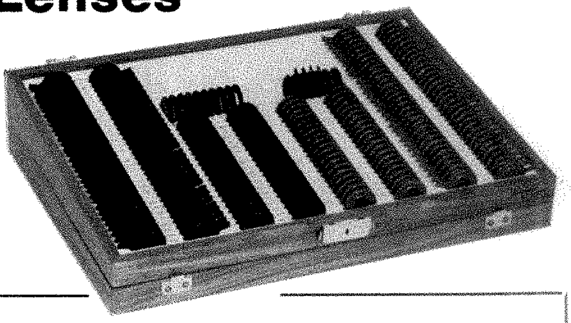

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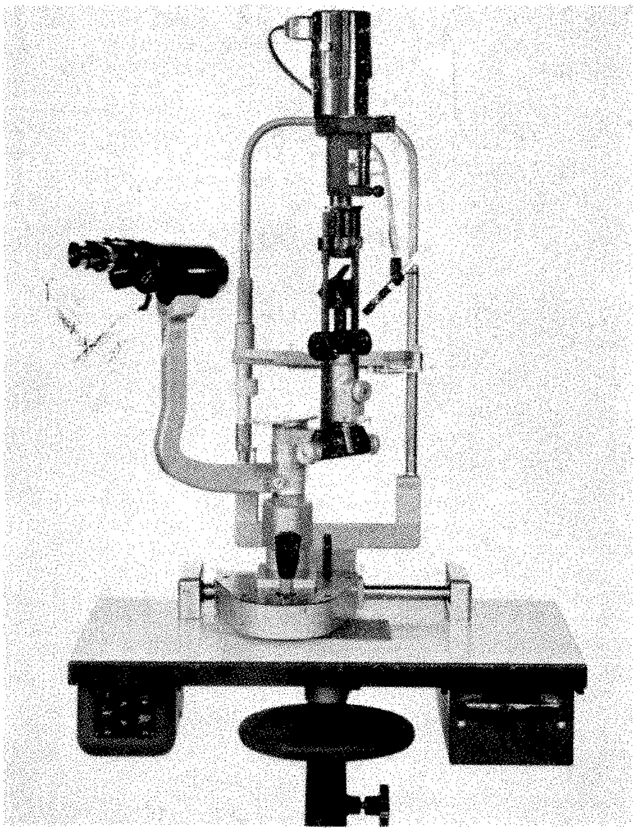

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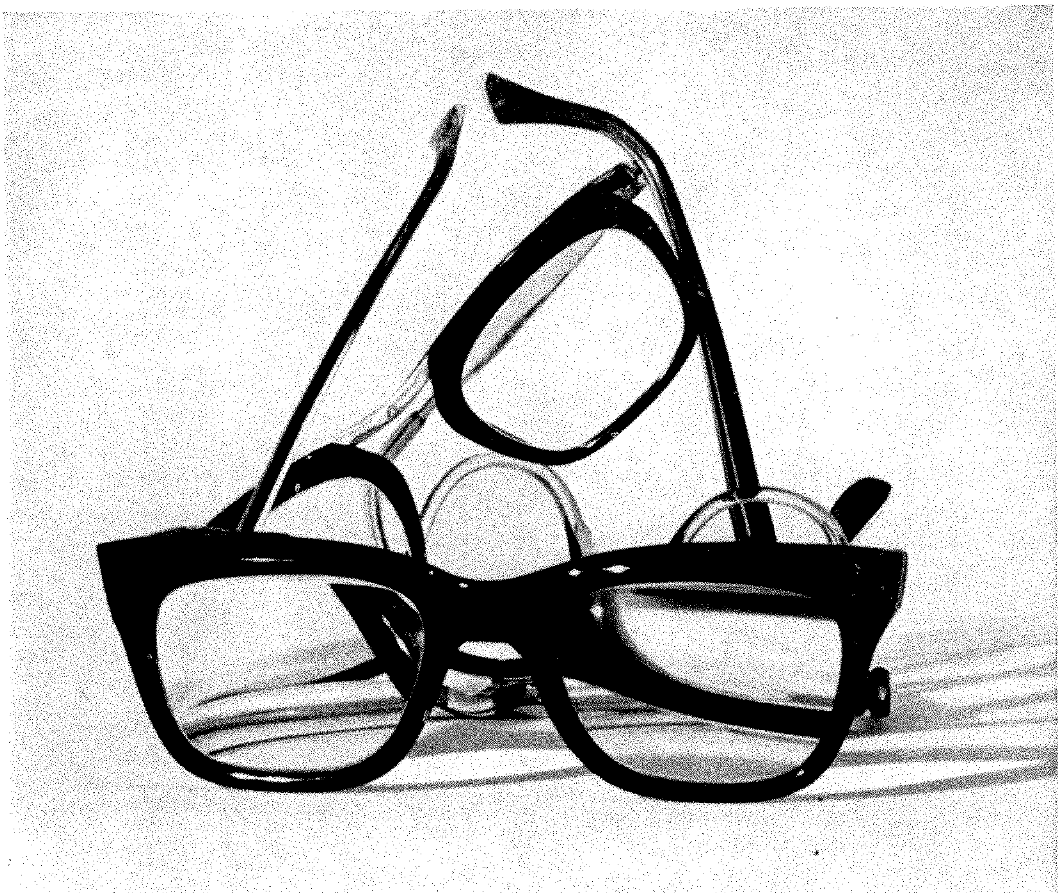

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The Merck Manual of Diagnosis and Therapy, 11th Edition, Merck Sharp & Dohme Research Laboratories, Rahway, 1966, p 512

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Brit. J. Ophthal. (1970) **54**, 145

Communications

Choroidal melanomata

Fluorescence angiographic and histopathological study

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This clinico-pathological study has been carried out on benign and malignant choroidal melanomata with the following objects in view:

(1) To find out the fluorescent pattern on fluorescence angiography which would distinguish a pigmented choroidal malignant melanoma from other lesions of similar appearance in the fundus of the eye, *e.g.* pigmented benign choroidal melanoma or non-neoplastic pigmentation.

(2) To study the pattern in non-pigmented malignant choroidal melanomata which could be confused with choroidal haemangiomata.

(3) To find out the pathological basis of the fluorescent pattern seen in benign and malignant choroidal melanomata.

(4) To find out the true nature of a benign choroidal melanoma, *i.e.* whether the pigmentation is always choroidal or is due in some cases to hyperplasia of the pigment epithelium.

MATERIAL AND METHODS

(A) FLUORESCENCE ANGIOGRAPHIC STUDIES

These were carried out in 38 patients who were seen with the following lesions at Moorfields Eye Hospital, City Road Branch, London:

(*i*) Benign choroidal melanomata (fifteen patients);

(*ii*) Flat pigmented malignant choroidal melanomata (fifteen patients);

(*iii*) Very lightly pigmented or amelanotic malignant choroidal melanomata (five patients);

(*iv*) Choroidal haemangiomata (three patients).

(B) HISTO-PATHOLOGICAL STUDIES

These were carried out at the Pathology Department at the Institute of Ophthalmology, London. The material included the following:

(*i*) Benign choroidal melanomata (thirty eyes);

(*ii*) Malignant choroidal melanomata (fifty eyes).

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OBSERVATIONS AND COMMENTS

(A) FLUORESCENCE ANGIOGRAPHIC STUDIES

I. **Benign choroidal melanomata** (BCM) (15 patients)

The pigmented lesion was noticed in the course of a routine ophthalmoscopic examination; it was situated at the posterior pole in all except two cases in which it was near the equator.

Fluorescence angiographic pattern (Fig. 1) During the transit of fluorescein, the background choroidal fluorescence in the area of the BCM is usually slightly less than elsewhere. During the late arterio-venous phase, the masking of the choroidal fluorescence is at its minimum at the site of the lesion. In one case, in which it was possible to outline the choroidal vascular bed during the very early stage of the transit, before the filling of the retinal arteries, the size of the lesion was found to be much greater than that revealed by ophthalmoscopy. As soon as the rest of the choroidal bed was filled, the non-fluorescent area diminished to a much smaller size (Fig. 1*b*). Late phases, 10–15 minutes after the injection of fluorescein, usually showed some degree of diminished fluorescence at the site of the lesion (Fig. 1*c*). In subjects with normally large amounts of pigment in the choroid, the BCM may show no significant diminution of choroidal fluorescence.

Drusen of variable number and size were seen in the lesion in only a third of the patients. These were usually outlined during the transit of the dye and in the late phase (Fig. 1*c*).

In one patient, the lesion was jet black and was due to hypertrophy of the pigment epithelium. It completely masked the background choroidal fluorescence. Thus, *when the pigmentation is in the choroid, it does not completely mask the choroidal fluorescence but reduces its intensity; however, when the pigmentation is in the pigment epithelium, it completely masks the choroidal fluorescence.*

II. **Malignant choroidal melanomata** (MCM)

(*1*) *Flat-looking pigmented malignant choroidal melanomata*

This group includes fifteen confirmed cases of MCM. The lesion in all of them was flat or only slightly raised. In the vast majority small yellowish-white non-pigmented patches were distributed in the dark grey pigmented lesion (Fig. 2*a* and 3*a*). The non-pigmented areas occurred more often in the peripheral part of the lesion, and quite often gave a striped appearance to the region of the tumour. Sometimes these patches were ill-defined. On follow-up, new non-pigmented spots appeared in previously pigmented areas as the tumour infiltrated at the periphery. The centre of the tumour in about a third had a greyish-white appearance and was usually more elevated than the peripheral areas.

Fluorescence angiographic patterns (Figs 2 and 3) During the transit of fluorescein through the vessels, the pigmented areas showed fluorescence which appeared in either the arterial or the early arterio-venous phase and tended to reach its maximum during the late arterio-venous phase, being less in the late venous phase. The non-pigmented areas showed either no fluorescence or much less fluorescence than that in the pigmented areas. Usually the difference in fluorescence of the pigmented and non-pigmented areas was quite marked. During the late arterio-venous phase or in the subsequent venous phase, small round discrete spots appeared in the lesion in all except two patients. These spots were more often situated in the peripheral part but could be seen anywhere in the lesion. Their number and fluorescence increased with the passage of time.

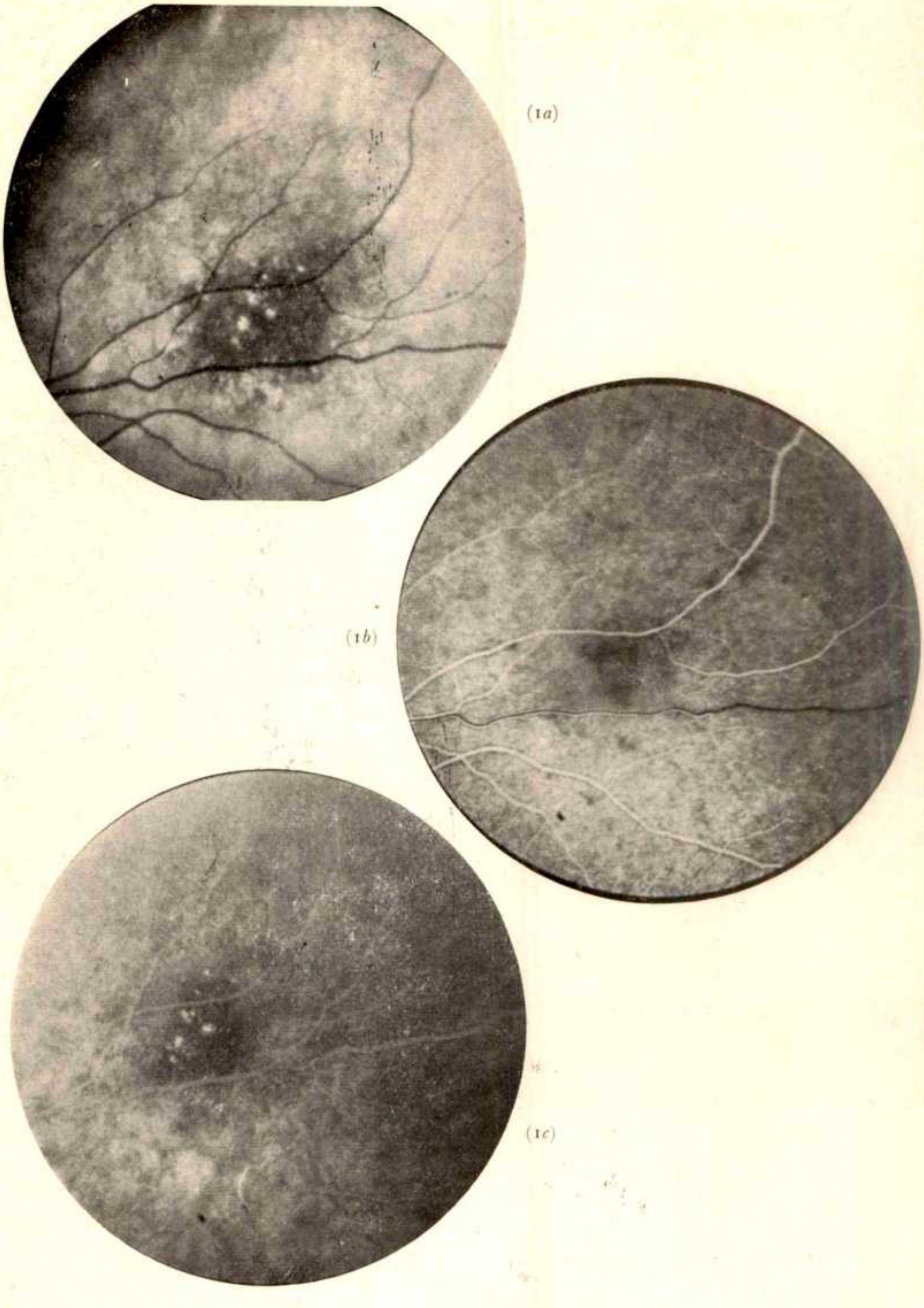

FIG. 1 *Benign choroidal melanoma in a 57-year-old woman*

(*a*) Ordinary fundus picture; (*b*, *c*) fluorescence angiograms during early arterio-venous (*b*) and late (*c*) phases. Note fluorescent drusen in (*c*).

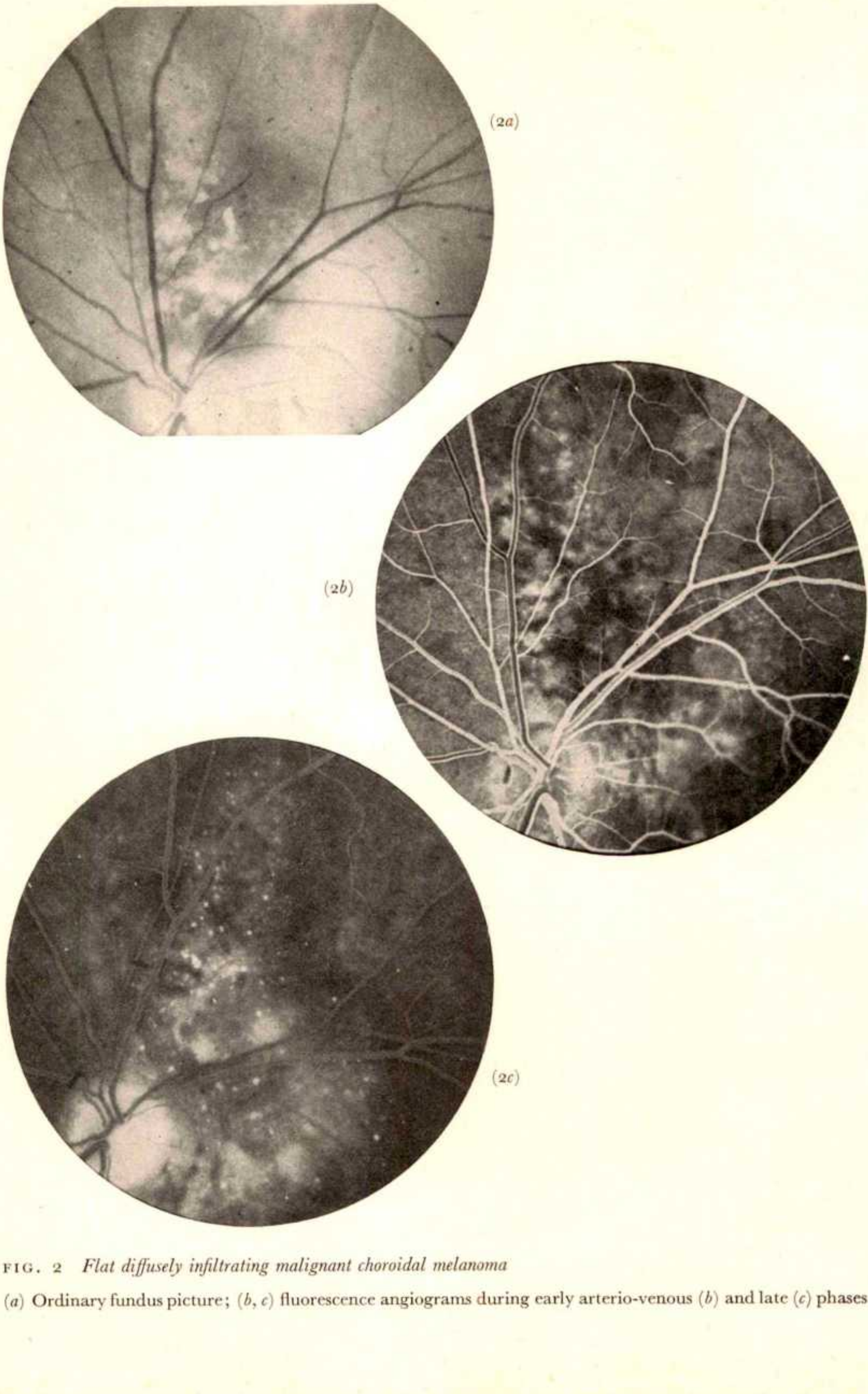

FIG. 2 *Flat diffusely infiltrating malignant choroidal melanoma*

(*a*) Ordinary fundus picture; (*b*, *c*) fluorescence angiograms during early arterio-venous (*b*) and late (*c*) phases.

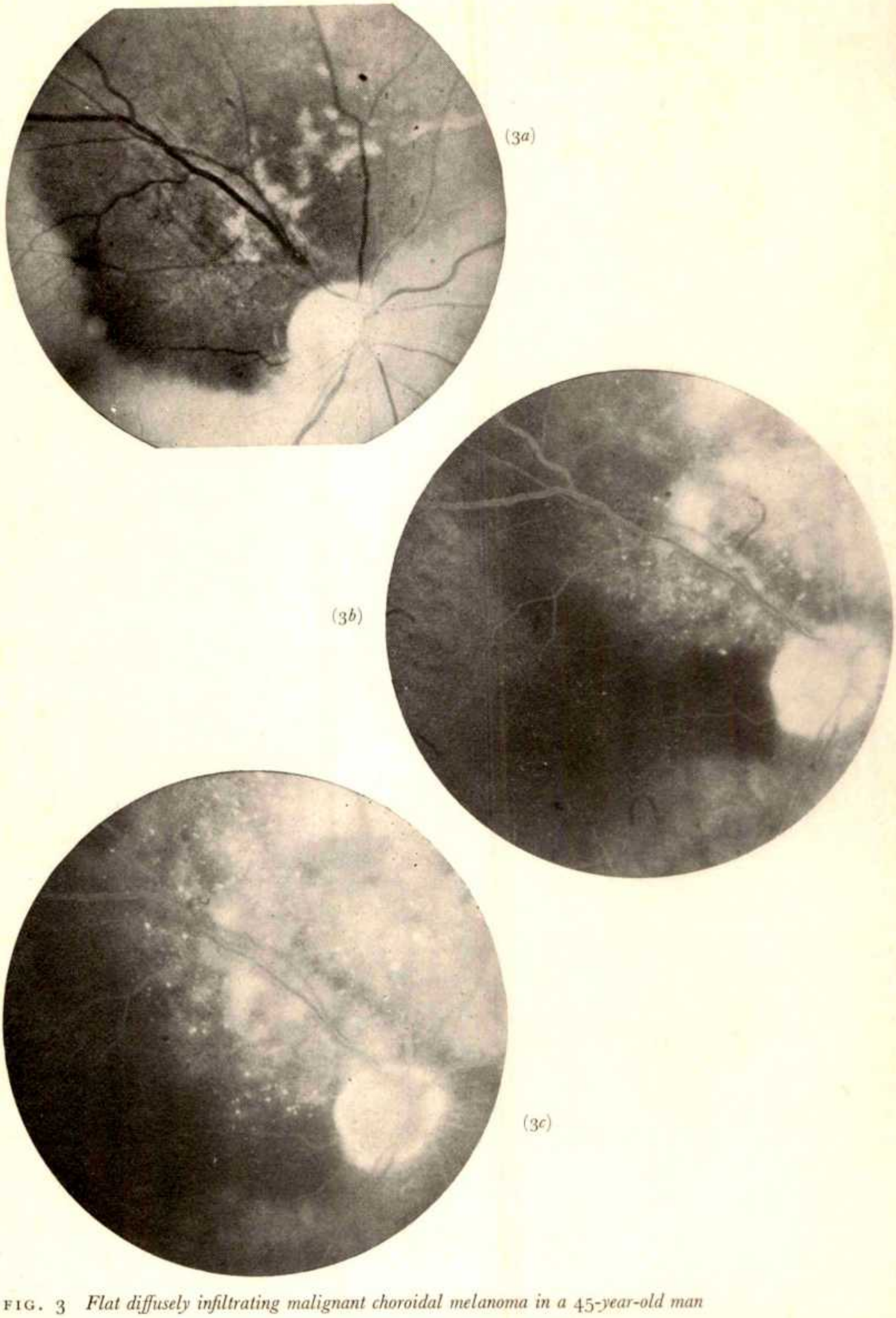

FIG. 3 *Flat diffusely infiltrating malignant choroidal melanoma in a 45-year-old man*

(*a*) Ordinary fundus picture at the time of the first fluorescence angiogram (*b*); (*b*, *c*) fluorescence angiograms during late phases, (*c*) 4 months after (*b*). Note an increase in size of lesion in (*c*).

During the late phase 10–15 minutes after the last injection of the dye, the lesion showed fluorescence due to staining with fluorescein. The fluorescent area was quite often smaller than the pigmented area seen ophthalmoscopically. The fluorescence tended to be marked at this stage. The difference in the intensity of fluorescence seen during the transit of the dye in pigmented and non-pigmented areas of the lesion tended to be less distinct during the late phase because of a diffuse fluorescence of the lesion, altough in some the pattern could still be made out. The peripheral part of the lesion in some tended to mask the background fluorescence (Fig. 3*a*, *b*). The small fluorescent spots were usually seen distinctly although in some these were not so clearly outlined because of diffuse fluorescence. The central white area, when present, was markedly fluorescent and in some cases was the only area showing significant fluorescence. During the transit of the dye such a central area usually showed less fluorescence and sometimes none.

In one case, haemorrhages in a lightly pigmented MCM produced a dark bluish-green colour with a non-pigmented area of the tumour in one part, confusing the lesion with a darkly pigmented MCM. In this case, the haemorrhage masked the fluorescence which was seen only in the non-pigmented area and became more marked in the later phases.

In contrast to the above-mentioned fluorescence pattern in MCM, in *non-neoplastic pigmented lesions of various aetiologies*, the pigmented areas were non-fluorescent while the non-pigmented areas fluoresced (Fig. 4)—a reverse of the MCM pattern. The intensity of fluorescence ran parallel with the choroidal fluorescence, reaching its maximum in the arterio-venous phase. During the late stages, after 10–15 minutes, the fluorescence was usually insignificant and, when present, was more marked in the non-pigmented areas. On the other hand, in MCM the late fluorescence was usually prominent and tended to be more marked in the pigmented areas except when there was a central whitish area which became markedly fluorescent.

There were, however, some pigmented non-neoplastic lesions in which the pigmented areas were more fluorescent than the non-pigmented areas (Fig. 5); this appearance resembled that of the MCM but the following points would differentiate the two lesions:

(*a*) The pigmented area showed a granular type of fluorescence which ran parallel to the choroidal fluorescence, reaching its maximum in the arterio-venous phase (Fig. 5*b*).

(*b*) The lightly pigmented or non-pigmented areas showed little or less fluorescence during the transit of the dye.

(*c*) In late stages, the pigmented areas showed little fluorescence while the light or non-pigmented areas showed fluorescence (Fig. 5*c*).

Late fluorescence would thus differentiate them from the MCM, and whenever there was doubt about the nature of a flat pigmented lesion, I have attached great significance to the following distinguishing features in trying to differentiate the flattish pigmented MCM from other pigmented lesions:

(*a*) In MCM the pigmented areas show fluorescence while the non-pigmented areas show much less or no fluorescence during the transit of the dye and usually in late fluorescence also.

(*b*) In MCM discrete small, round fluorescent spots usually appear in the lesion, more often in the peripheral part. These usually appear in the venous phase and tend to become more prominent and numerous as time passes. In one case, repeated angiography showed that the old spots had disappeared and a new batch of spots had appeared (Fig. 3).

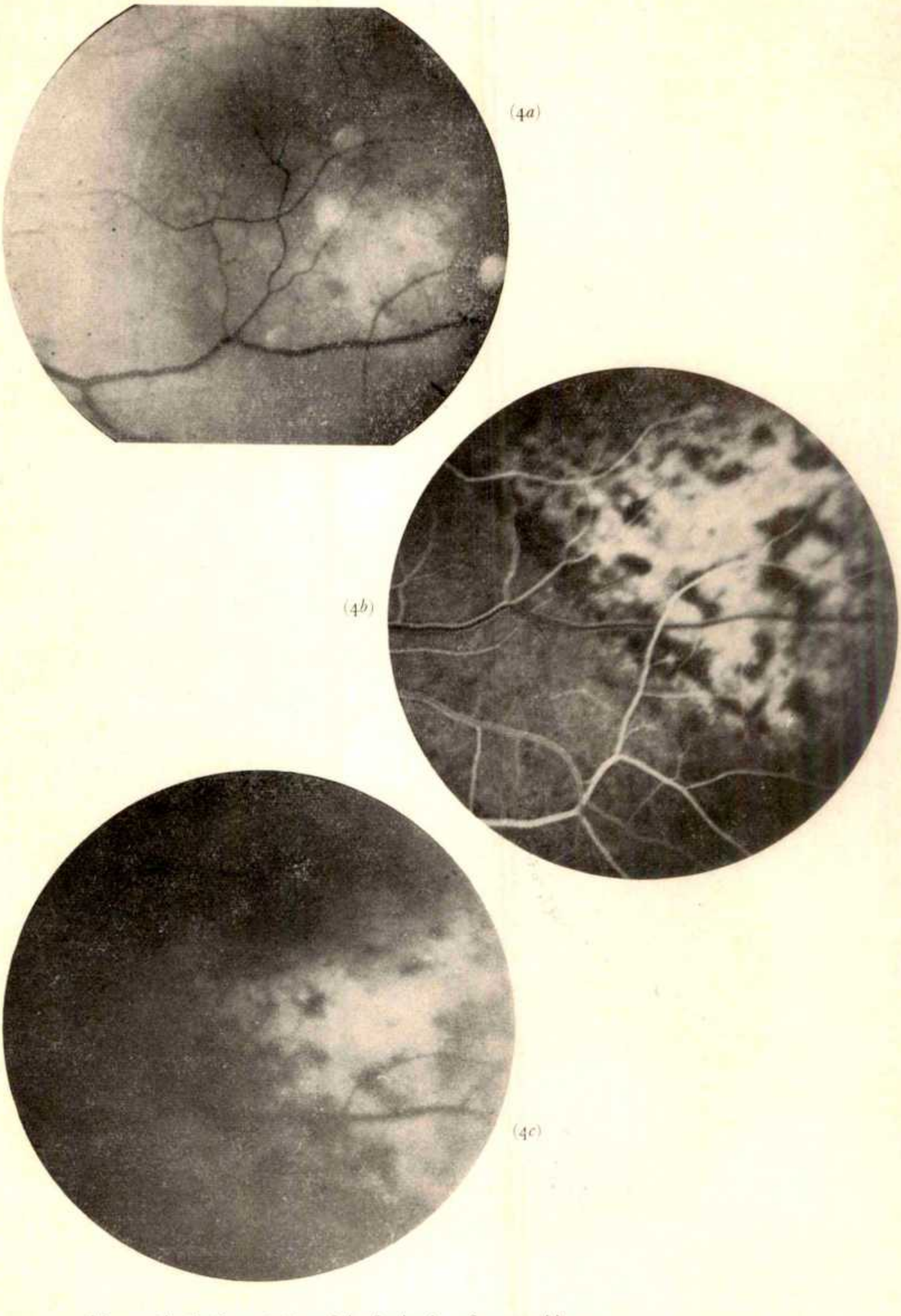

FIG. 4 *Non-neoplastic pigmentation of the fundus in a 60-year-old man*

(*a*) Ordinary fundus picture; (*b*, *c*) fluorescence angiograms during early arterio-venous (*b*) and late (*c*) phases.

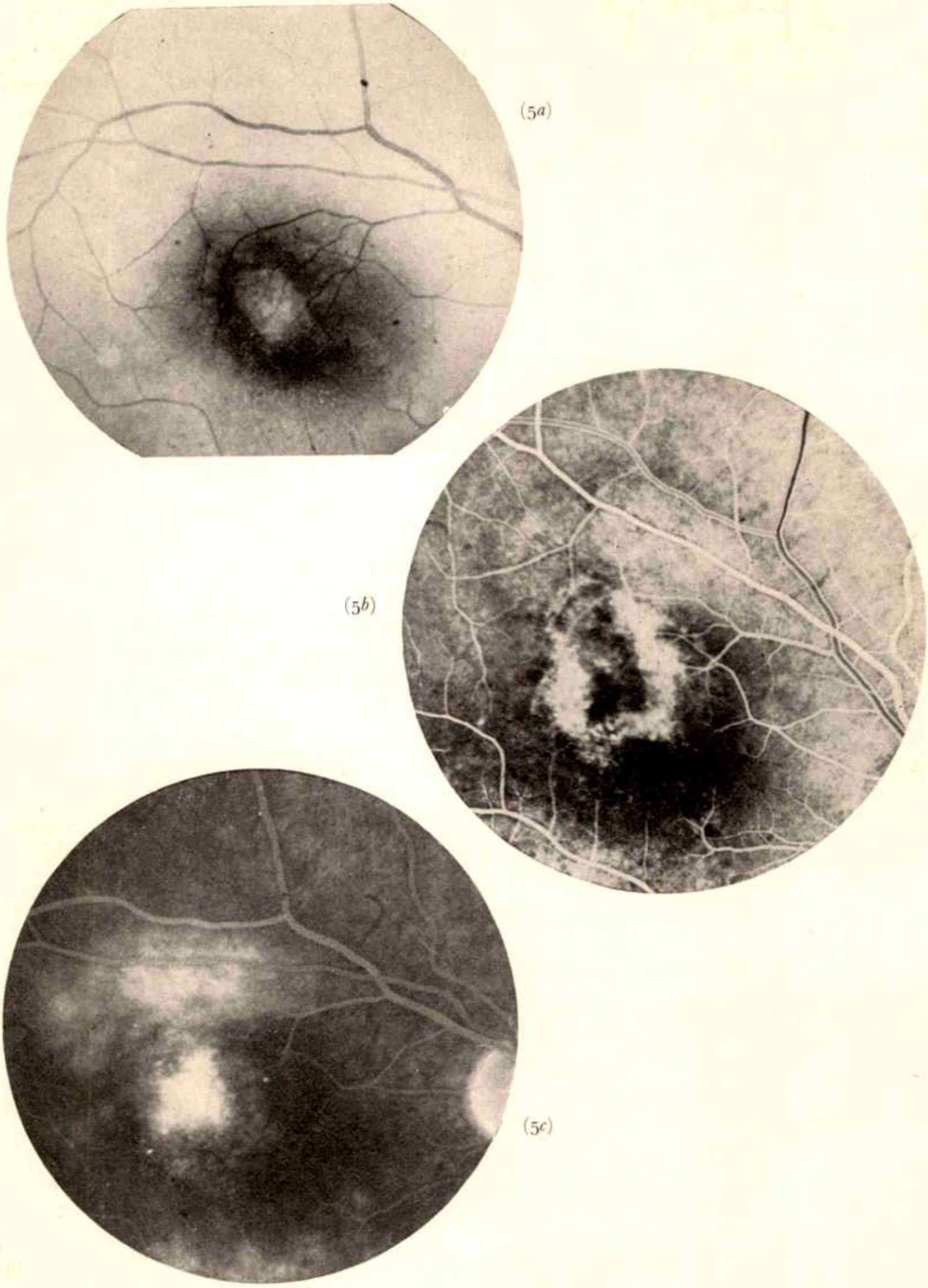

FIG. 5 *Non-neoplastic pigmentation of macular region in a 41-year-old man*

(*a*) Ordinary fundus picture; (*b*, *c*) fluorescence angiograms during early arterio-venous (*b*) and late (*c*) phases. Note the leakage of fluorescein above and below the lesion due to abnormal retinal capillaries.

(2) *Non-pigmented malignant choroidal melanomata*

This group consists of five cases with large non-pigmented tumours projecting into the eye. Histopathological examination confirmed that all were MCM. The tumour surface was pink or white in colour or a mixture of the two, with white areas scattered on the surface. In four cases prominent choroidal vessels were visible on some part of the surface of the tumour (Fig. 6); they had perforated Bruch's membrane and the pigment epithelium as was shown by histopathology.

Fluorescence angiographic pattern (Fig 6) During fluorescein transit, the fluorescence of the lesion was seen to be more marked in the pinkish areas than in the white areas. The fluorescence tended to appear with the arterial phase of the retinal circulation. On rare occasions the tumour became fluorescent only gradually and progressively. With the passage of time, the fluorescence increased. The prominent vessels seen on the surface beneath the retinal vessels filled at the same time as the retinal arteries or a little before, or at the same time as the retinal veins. This may depend upon the nature of the vessels, *i.e.* whether they are arterial or venous in nature. These abnormal vessels were choroidal and the larger ones were found to be markedly permeable to the dye, so that fluorescein leaked out rapidly (Fig. 6*b*), giving them a feathery appearance. This demonstrates the mechanism responsible for staining the tumour tissue on fluorescence angiography. In these amelanotic MCM, if light grey patches were seen on the surface, they were non-fluorescent in contrast to the pigmented MCM.

The lesion showed marked late fluorescence of a diffuse nature (Fig. 6*c*), the pure white lesions being much more fluorescent in late pictures than during the transit.

The tumours could be confused with choroidal haemangiomata or a secondary tumour deposit in the choroid.

A pink tumour showing patchy fluorescence during the pre-arterial phase of retinal circulation would favour the diagnosis of choroidal haemangioma. Other clinical signs would assist in such a differentiation. The choroidal haemangioma is usually located close to the optic disc (Fig. 7); it is lighter in colour than the remainder of the fundus with no pigment in it, and is lighter than the remaining fundus on retroillumination, and shows sector-shaped field defects. Some of the secondary deposits are non-fluorescent, and when they are fluorescent their fluorescence pattern tends to be of a different type.

III. Choroidal haemangiomata

This group includes only three cases which may seem too few for definite conclusions to be drawn. One was an almost exact replica of another, *i.e.* they were both situated superiorly and close to the optic disc, were moderately elevated, and had pinkish surfaces and big whitish irregular patches (Fig. 7). The third was seen in a young woman aged 20 years; it was nasal to the disc and much larger than the other two, having a pink colour with white patches on the surface. Unlike the amelanotic tumours there was a gentle slope from the swelling to the adjoining normal retina. No retinal detachment was seen in any of these cases.

Fluorescence angiographic pattern (Fig. 7) During the fluorescein transit these choroidal haemangiomata showed patchy fluorescence before the dye reached the retinal arteries, and it was much more intense as the transit of the dye progressed. The white patches masked the fluorescence of the lesion to some extent, so that the pink areas were more fluorescent than the white areas. No choroidal vessels were seen.

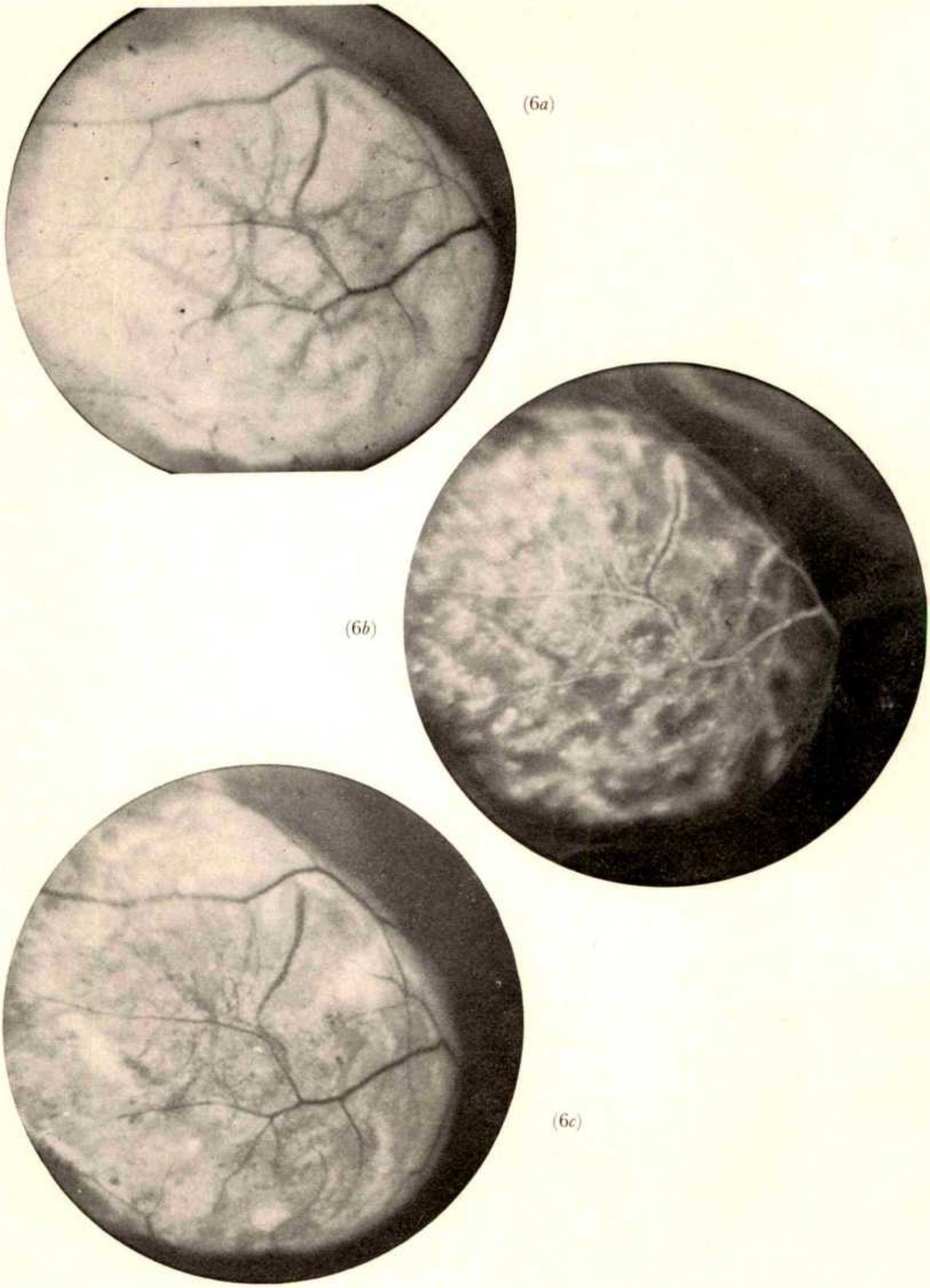

FIG. 6 *Malignant choroidal melanoma in a 52-year-old man which has perforated Bruch's membrane and the pigment epithelium*

(*a*) Ordinary fundus picture; (*b*, *c*) fluorescence angiograms during arterio-venous (*b*) and late (*c*) phases.

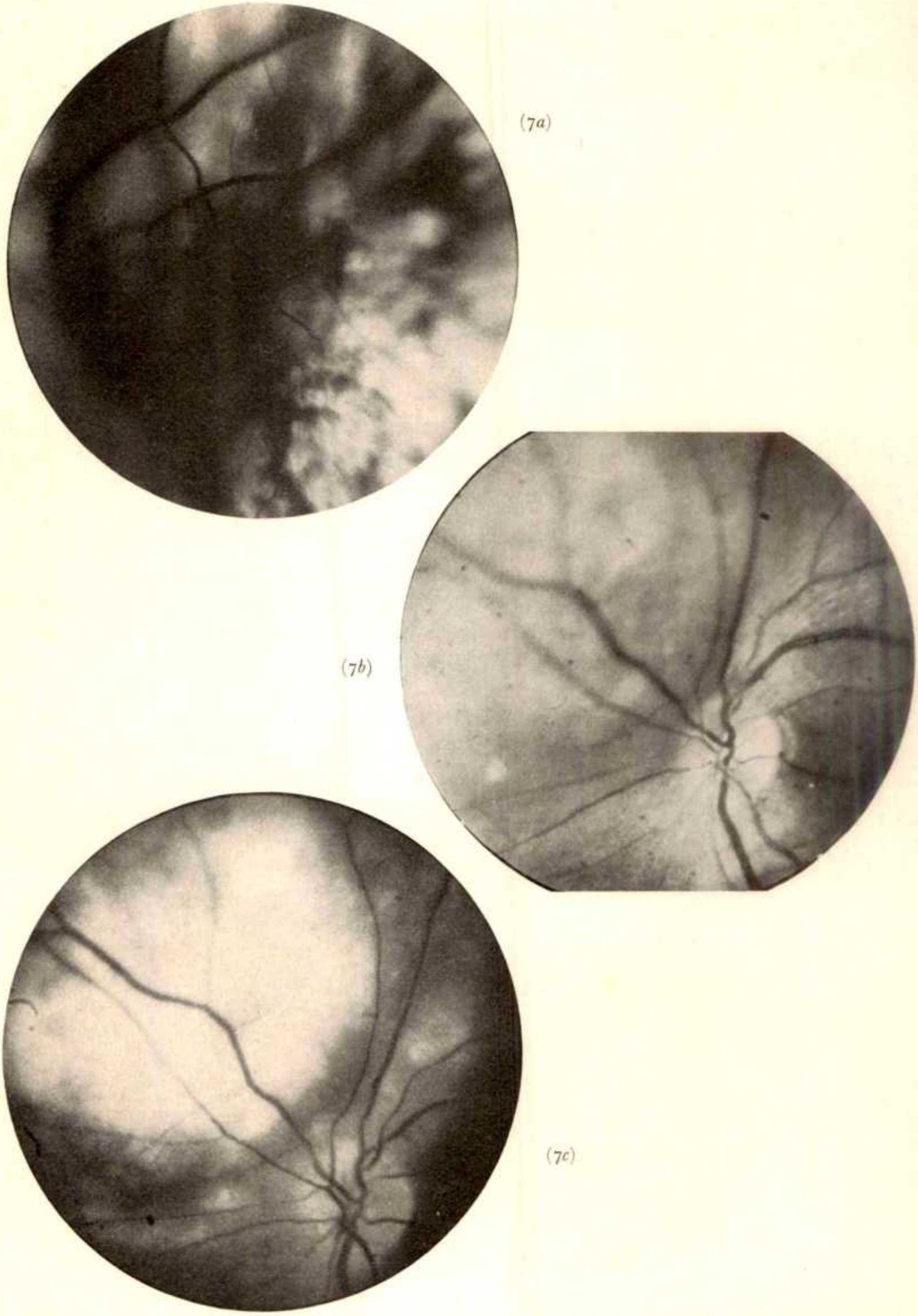

FIG. 7 (a) *Fluorescence angiogram of choroidal haemangioma in a 20-year-old woman during pre-arterial phase of retinal circulation.* (b, c) *Choroidal haemangioma in a 49-year-old man.* (b) *Ordinary fundus picture.* (c) *Fluorescence angiogram during late phase*

In the first two cases, on the slope of the retina at its margins, the retinal capillaries, which were prominent and dilated, leaked fluorescein as the dye was passing through them. This produced a spotty fluorescence around the haemangioma.

Late pictures, 10–15 minutes after injection, showed fluorescence of the lesions; in the first two cases this was less in the white than in the pink areas, and around the lesion there was a small rim of minor fluorescence which was surrounded in turn by a band of patchy fluorescence caused by the leakage from the retinal capillaries (Fig. 7*c*).

Some may be of the opinion that these lesions could be amelanotic melanomata. The third patient in this group has been followed for nearly 15 years since she was 5 years old, and has esotropia in this eye. In the first patient, the lesion was once treated with light coagulation; this immediately collapsed the tumour which is unlike a MCM. The second patient came from Cyprus and I have lost contact with her, but I presume that the tumour was a haemangioma, being an exact replica of the first in all respects.

(B) HISTO-PATHOLOGICAL STUDIES

These have been carried out in the hope of discovering the pathological basis of the fluorescence patterns described above.

I. Benign choroidal melanomata

These included cases in which the eye was removed for some other ocular lesion, the BCM being an incidental finding. Thirty cases were studied to find out the site of the pigment deposition. In all these, the pigmentation was situated in the outer layers of the choroid and extended inwards to a variable extent, sometimes approaching the pigment epithelium (Fig. 8). However, a gap was always discernible between the choroidal pigmentation and the pigment epithelium. In none of these was hypertrophy of the pigment epithelium seen. In the vast majority the lesion was in the posterior half of the globe, mostly at the posterior pole. The presence of colloid bodies over the lesion was a rare finding (Fig. 8). In some, the area of the lesion showed a vascular choroid with prominent choroidal vessels. Such a lesion would obviously be slightly elevated. The pigment epithelium and the retina over the lesion were normal in all cases where no other pathological lesion, unassociated with BCM, was considered to be responsible for changes in these.

II. Malignant choroidal melanomata

Histological sections from fifty cases with MCM were studied. The investigation was primarily concentrated on a study of the state of the pigment epithelium over the tumour in order to find out the factors responsible for the fluorescence pattern of the MCM. In all cases the pigment epithelium overlying the tumour was abnormal, showing degenerative and disintegrative changes in some places and being totally absent in others (Fig. 9*a*). In about half the cases, the pigment epithelium showed one or more small patches of thickening of the pigment epithelium over the tumour, usually near its periphery. Some of these seemed to be due to hypertrophy and others to aggregation of the pigment (Fig. 9*a*). In some places hyaline degeneration was seen in the pigment epithelium. Rarely, a few small tumour pieces which were separate from the main tumour mass could be seen between the retina and the pigment epithelium. The overlying Bruch's membrane showed colloid bodies in some cases. Small localized areas of subepithelial and/or subretinal exudation were also seen over the tumour.

In some of these cases, the tumour tissue lay in the centre with a mantle of choroidal pigment around it, as if the malignant change started in the centre of a BCM and its growth

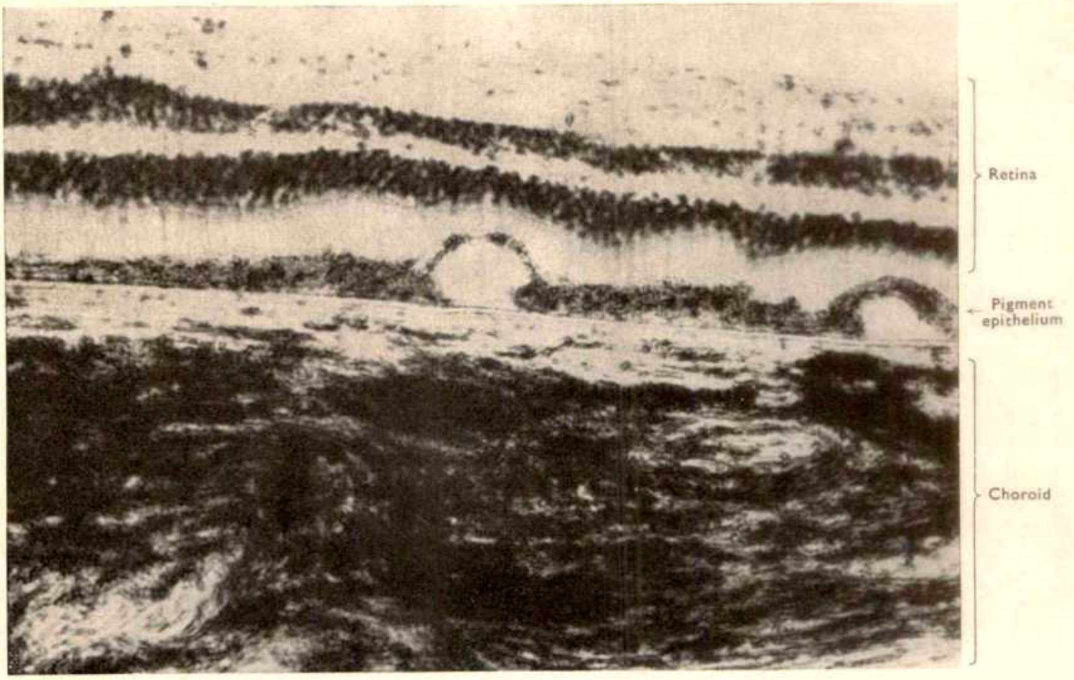

FIG. 8 *Photomicrograph of a benign choroidal melanoma; note the two drusen on Bruch's membrane*

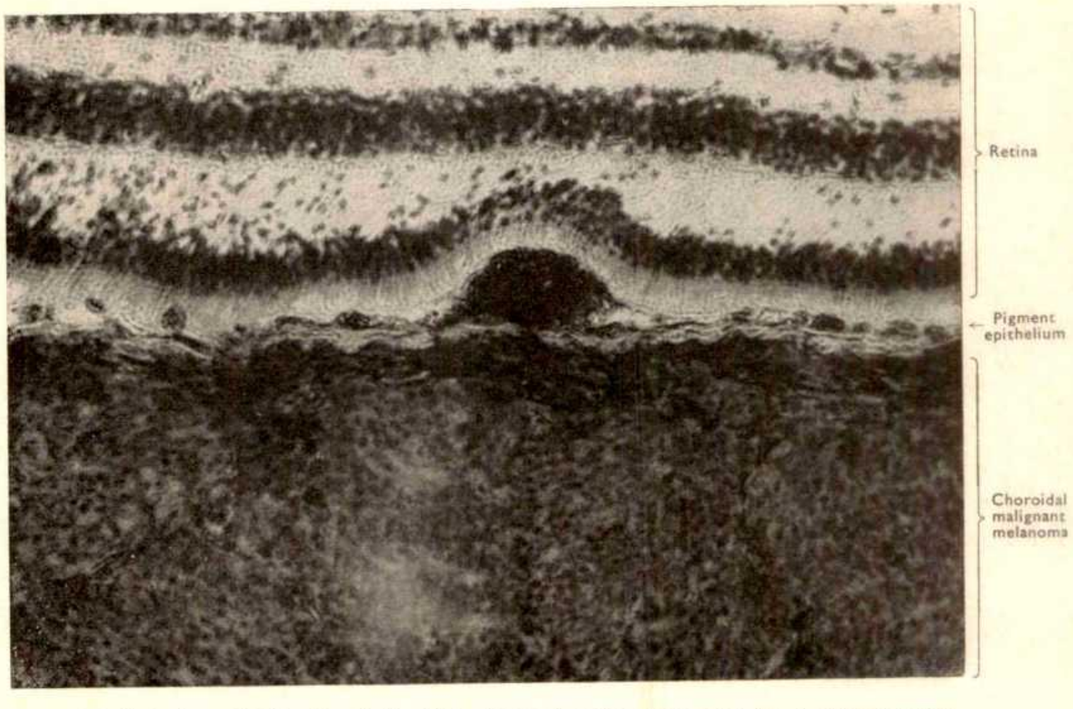

FIG. 9 (*a*) *Photomicrograph of malignant choroidal melanoma from the tumour seen in Fig. 2, showing aggregation of pigment at one site with degenerative changes at other sites in the pigment epithelium.*

pushed the original pigment outwards around it. Thus, at its peripheral margins, there was a considerable amount of the BCM type of pigmentation which may have been responsible for the reduced or absent background choroidal fluorescence at the periphery of the tumour.

From these histopathological studies, the following interpretations of the fluorescence pattern of the BCM and MCM could be postulated:

(1) In BCM it is the deposition of pigment in the choroid which is responsible for the ophthalmoscopic picture of the lesion. On fluorescence these choroidal lesions are partially but not completely non-fluorescent; the degree of non-fluorescence depends upon the extent of the involvement of the choroid by the pigment. If the pigment involves only the external part, it may show normal fluorescence or only slightly reduced fluorescence as compared with the surrounding fundus. When the pigment involves most of the thickness of the choroid, the fluorescence is markedly reduced; fluorescein in the chorio-capillaris is responsible for some fluorescence still present. In contrast, when there is hypertrophy of the pigment epithelium, there is a complete masking of the choroidal fluorescence and no partial fluorescence of the lesion is seen. From the histological sections, it was not possible to determine the exact extent of involvement of the chorio-capillaris. I feel that when the pigment does not involve the chorio-capillaris, the lesion will not be associated with any field defect. But when it involves the overlying chorio-capillaris it leads to field defects. Such visual field defects with BCM have been recorded by Tamler and Maumenee (1959: in 38 per cent.), by Naumann, Yanoff, and Zimmerman (1966), by Karickhoff (1967: in 21 per cent.), and by Flindall and Drance (1969: in 85 per cent.). Flindall and Drance (1969) speculated that the field defects were due to derangement of the pigment epithelium or outer segments of rods and cones without microscopical changes. The incidence of drusen over a BCM, so much stressed in the literature, is not common, as is shown by both the fluorescence and the histological studies. Naumann, Zimmerman, and Yanoff (1966) recorded, in 41 per cent. of their cases, changes in the overlying tissue, which included narrowing or obliteration of the chorio-capillaris, changes in the pigment epithelium, drusen, and retinal lesions. In the present series, no significant changes were seen in the pigment epithelium and the retina apart from the occasional drusen.

(2) The fluorescence of the lesion in the MCM is due to two factors:

(*a*) Disintegration or even complete absence of the overlying pigment epithelium leads to unmasking of the background fluorescence of the choroid.

(*b*) The tumour is usually very vascular. When a tumour perforates Bruch's membrane and the pigment epithelium, so that tumour tissue is clearly visible through the clear retinal tissue, a large number of prominent vessels are almost always seen. Moreover the vessels in the tumour are abnormal (Fig. 9*b*) and abnormally permeable to fluorescein, leading to a marked outflow of fluorescein from the vessels into the tissue.

Thus, in MCM, the characteristic fluorescence of the lesion is due to increased vascularity, abnormally permeable choroidal vessels, and disappearance of the overlying pigment epithelium. In patients with MCM treated by cobalt plaque by Mr. M. A. Bedford at Moorfields Eye Hospital, I have carried out fluorescence angiography both before and after treatment. Although a large amount of the pigment is left at the site of the lesion after treatment, fluorescence is completely absent all along. In fact, no vessels are seen in that area and for some distance surrounding the lesion after the cobalt radiation treatment; for some distance beyond it only the very large choroidal vessels are seen. This seems to

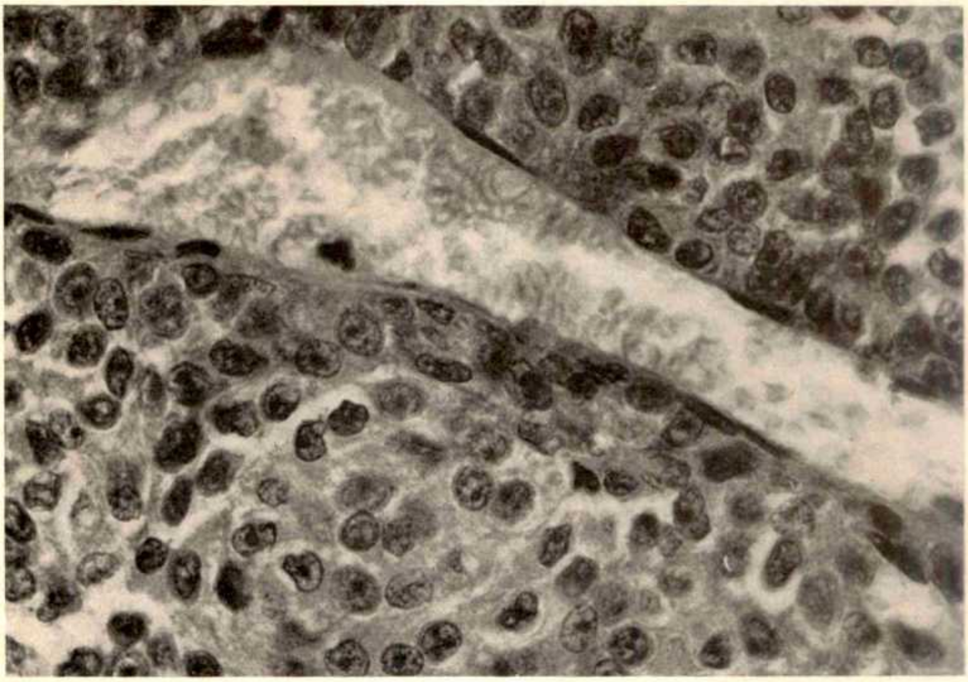

FIG. 9 (*b*) *Photomicrograph of malignant choroidal melanoma, showing one of the abnormal vessels seen in Fig. 6*

indicate that the fluorescence of the MCM is due to its abnormal vascularity and that the pigment itself has no part in it.

(*c*) In most of the pigmented MCM of this series, there were non-pigmented patches in the pigmented parts, producing a mottled appearance. It is not possible to be definite about the nature of these patches, but the histological studies suggest that they may be caused by a patchy thickening of the pigment epithelium. This is further supported by the observation that these non-pigmented patches remain non-fluorescent when the pigmented part becomes fluorescent after the injection of fluorescein. Such a hypertrophy of the epithelium was not seen in histological sections over a benign melanoma.

(*d*) The exact nature of the small round discrete fluorescent spots observed in the pigmented tumours is not clear. They may be due to small localized areas of subretinal/subepithelial exudation or to drusen in Bruch's membrane, or they may possibly be caused by extension of the tumour tissue which comes to lie between the pigment epithelium and the retina. The last phenomenon, *i.e.* extension of the tumour, was only very rarely seen in histological sections in the present study; it was much less frequent than the spots seen in fluorescence angiography. Moreover, the number and site of the spots changed at successive examinations, suggesting that they represented small localized exudates under the retina or the pigment epithelium.

The MCM are always accompanied by a localized visual field defect. I feel that this may be due to changes in the pigment epithelium which is always involved in MCM, and to involvement of the chorio-capillaris in the tumour. At a later stage the complete absence of Bruch's membrane and of the pigment epithelium and the associated retinal degeneration and detachment, would make the field defect more pronounced. Later still the defect would be due to invasion of the retinal tissue by the tumour.

CONCLUSIONS AND SUMMARY

This study has been carried out by fluorescence fundus angiography in 38 patients and histopathological examination in eighty eyes with benign or malignant choroidal melanomata.

On fluorescence angiography, the benign choroidal melanoma showed a variable degree of masking of the background choroidal fluorescence which depends upon the extent of infiltration of the choroid by the pigment.

A flat diffusely infiltrating malignant choroidal melanoma (MCM) has small yellowish non-pigmented patches scattered on its surface, more at the periphery. On fluorescence angiography, the pigmented areas are fluorescent and the non-pigmented areas are non-fluorescent. Usually, these also show numerous small round discrete fluorescent spots. Non-neoplastic lesions of similar appearance show two types of fluorescence pattern. In the first group, the pigmented areas are non-fluorescent and non-pigmented areas are fluorescent. In the second group, during the transit of the dye, the pigmented areas are fluorescent and non-pigmented areas are non-fluorescent, but during the late phase the pigmented areas are non-fluorescent or faintly fluorescent but the non-pigmented areas are markedly fluorescent.

In an amelanotic choroidal melanoma, the pink areas fluoresce more than the white areas during the transit of the dye and the reverse occurs during the late phases. Abnormal choroidal vessels, when seen, usually show a marked leakage of fluorescein. The lesions are markedly fluorescent.

In choroidal haemangioma, patchy fluorescence is seen during the pre-retinal-arterial phase, with leakage of fluorescein at a later stage.

Histopathologically, the pigment epithelium over the malignant choroidal melanoma was never normal. The epithelium was either degenerate or absent. In about half the cases examined a few small patches of thickened pigment epithelium were seen. In the benign choroidal melanoma, no change was seen in the pigment epithelium over the area of choroidal pigmentation; the latter involved the choroid to a variable thickness extending from the periphery inwards. A thin layer of chorio-capillaris was usually not involved by the pigment.

Fluorescence of the malignant choroidal melanoma is due to the partial or complete absence of the pigment epithelium over the tumour, marked vascularity, and abnormally permeable vessels in the tumour.

I am grateful to Prof. Barrie R. Jones and Prof. Norman Ashton for the facilities provided; to the various ophthalmologists who referred the patients, particularly Mr. M. A. Bedford; to the Audiovisual Department of the Institute of Ophthalmology for the illustrations; and to Mrs. Susan Zimmerman for secretarial help.

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Aetiology of the anatomical basis for primary angle-closure glaucoma

Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma

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Shallowness of the anterior chamber received special attention after the demonstration by von Graefe (1857) that iridectomy could cure acute glaucoma. Bowman (1862) referred to the care required in performing iridectomies on eyes with shallow anterior chambers.

Over many years, and by careful dissections of cadaver and enucleated eyes, Priestley Smith (1891) concluded that the shallow anterior chamber occurred already before the disease (glaucoma), was an expression of disproportion between the size of the eyeball and the lens, and was an important aetiological consideration for glaucoma.

Using Lindstedt's apparatus, accurate anterior chamber depth measurements were performed on large numbers of living eyes by Rosengren (1931, 1950), who showed that shallow anterior chambers predisposed to acute congestive glaucoma and that the shallowness existed before the increase of pressure and was not a consequence of it. In the same person, measurements of the affected and fellow eyes were practically identical.

Barkan (1954) was able to describe fully the mechanics of primary angle-closure glaucoma and the dependence of the relative pupil block upon a forward position of the anterior lens surface. However, explanations of the shallow anterior chamber remained unsatisfactory.

Many patients with shallow anterior chamber glaucoma were found to be hypermetropic, and as anterior chambers tend to be more shallow in hypermetropia than in emmetropia, and especially different from myopia where anterior chambers are usually deep, many authors referred to angle-closure glaucoma as occurring in "small hypermetropic eyes" (these papers are reviewed by Törnquist, 1953).

Correlations between anterior chamber depths and refractive errors have been demonstrated by many investigators (Stenström, 1946). Weekers and Grieten (1961) confirmed the correlation between anterior chamber depth and refractive error provided cases of "complicated myopia" were excluded, but for myopia greater than 5 dioptres no correlation was found between refractive error and anterior chamber depth. Grieten and Weekers (1962) showed further that the mean measurements for eyes with angle-closure glaucoma gave anterior chambers 0·73 mm. more shallow, corneal curvatures 0·20 mm. less, and corneal diameters 0·48 mm. smaller than for eyes of the same age with the same degree of hypermetropia.

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Thus, although eyes with primary angle-closure glaucoma are mostly hypermetropic (Sugar, 1941; Lowe, 1961), nevertheless, some are myopic, so that hypermetropia is insufficient to explain the anatomical conditions that lead to the angle-closure glaucoma.

Investigations

61 patients who had primary angle-closure glaucoma and 80 persons of similar age and sex with normal eyes, were examined by all methods necessary for accurate diagnosis and appropriate management, as well as by keratometry (Haag-Streit), pachometry (Haag-Streit), and 15 M Hz. time amplitude ultrasonography. Details are given elsewhere (Lowe, 1967, 1968, 1969a). All eyes showing any significant abnormality due to the glaucoma or the surgery, and any with defects other than normal age changes were excluded.

For the subjects with angle-closure glaucoma, refraction records were compiled from measurements or spectacles obtained before any acute attacks. (The number of eyes with angle-closure glaucoma in the refractive error table is greater than the number in the other investigations because of the availability of some refractive records before eye damage from acute angle-closure glaucoma.)

Refractions

Table I shows the spherical equivalent of the spectacle refraction of 127 eyes with primary angle-closure glaucoma. This Table is similar to others published previously (Sugar, 1941; Lowe, 1961). Most of the eyes were virtually emmetropic when allowance is made for the normal increase of hypermetropia with age. Myopic eyes are very few but some are present.

Table 1 *Mean spectacle refraction of 127 eyes with primary angle-closure glaucoma*

Dioptres	0 to 1·0	1·25 to 2·0	2·25 to 3·0	3·25 to 4·0	4·25 to 5·0	5·25 to 6·0	6·25 to 7·0	7·25 to 8·0	8·25 to 9·0	*Over* 9·0
+	42	31	19	14	6	6	–	–	2	–
–	4	1	–	–	–	–	1	1	–	–

Comparison of means

Table II (opposite) presents a summary of comparisons of physical measurements between normal eyes and those with angle-closure glaucoma. Lavergne and Kelecom (1962) found corneal thickness to be the same for hypermetropic and myopic eyes, and Table II shows no significant difference between the mean central corneal thickness of the normal and glaucomatous eyes. The means of the other parameters show significant differences between the two groups of eyes, but although the means are so significantly different, the ranges show that there is overlap for some measurements from individual eyes in the two groups.

Table II *Summary of comparison of physical measurements between 157 normal eyes and 118 eyes with angle-closure glaucoma (Means with standard deviations)*

Series of eyes	157 *normal*		118 *with angle-closure glaucoma*		*t test between means*
Parameter	*Mean*	*Range*	*Mean*	*Range*	
Central corneal thickness	0·517 ± 0·34	0·41–0·60	0·533 ± 0·034	0·44–0·63	not significant
Corneal radius of curvature	7·67 ± 0·24	7·13–8·54	7·61 ± 0·29	6·96–8·31	significant
Anterior chamber depth	2·8 ± 0·36	2·1–3·6	1·8 ± 0·25	1·1–2·4	highly significant
Relative lens position	0·22 ± 0·012	0·1807–0·2405	0·20 ± 0·013	0·1413–0·2294	highly significant
Lens thickness	4·50 ± 0·34	3·7–5·4	5·09 ± 0·63	4·4–6·2	highly significant
Axial length	23·10 ± 0·82	20·7–25·3	22·01 ± 1·06	18·5–26·0	highly significant

All measurements shown in mm. except relative lens position $= \dfrac{\text{A.C. depth} + \frac{1}{2}\text{ lens thickness}}{\text{axial length}}$

Correlations with axial length

Table III presents the statistical correlations between axial length and various parameters for normal eyes and those with primary angle-closure glaucoma.

Martola and Baum (1968) could find no correlation between central corneal thickness and refractive error, and in this survey no correlation could be found between central corneal thickness and axial length for either type of eye.

Table III *Summarized statistics of various parameters* (X) v. *axial length* (Y) *of normal eyes and eyes with primary angle-closure glaucoma*

Series of eyes	157 *normal*				118 *angle-closure glaucoma*			
		Analysis of variance				*Analysis of variance*		
Parameter (X)	*Regression line slope*	*F—ratio*	*P*	*Significance*	*Regression line slope*	*F—ratio*	*P*	*Significance*
Central corneal thickness	−0·417	0·047	—	nil	−1·75	0·364	—	nil
Corneal radius of curvature	+1·54	39·7	<0·0005	extreme	+2·14	66·2	<0·0005	extreme
Anterior chamber depth	−1·19	60·2	<0·0005	extreme	0·71	3·5	0·1 > P > 0·05	not
*Relative lens position	+1·27	48·2	<0·0005	extreme	+0·53	2·1	>0·10	not
Lens thickness	−0·66	12·2	0·01 > P > 0·001	high	+0·011	0·002	—	nil

*Relative lens position $= \dfrac{\text{A.C. depth} + \frac{1}{2}\text{ lens thickness}}{\text{axial length}}$

The corneal radius of curvature shows extreme correlation with axial length in both types of eyes. As the cornea is part of the eyeball wall, a correlation might have been expected, and for primary angle-closure glaucoma the degree of correlation confirms that the cornea is a co-ordinated structure for eyeball size

In normal eyes, lens thickness is inversely and lens position directly correlated with axial length. These correlations are the main determinants of anterior chamber depth. Compared with eyes of average length, short eyes will tend to have thicker lenses sited more forwards, while long eyes will tend to have thinner lenses sited more posteriorly. This is in keeping with the inverse correlation between refractive errors and anterior chamber depth.

By contrast, in primary angle-closure glaucoma there is no significant correlation between thickness and position of the lens and axial length. In a previous paper (Lowe, 1969b), no correlation could be found between lens thickness and corneal radius of curvature for eyes with angle-closure glaucoma although a significant correlation was found for normal eyes. Thus in primary angle-closure glaucoma, although the cornea is a co-ordinated structure in relation to eyeball size, the lens is inco-ordinated in both its thickness and its position in relation to the eyeball walls. In primary angle-closure glaucoma, loss of co-ordination between lens and axial length shows as excessively thick and anteriorly sited lenses, which, in turn, produce shallow anterior chambers (Table II).

Correlations with age

Table IV presents statistical correlations between age (30 to 85 years) and various parameters for normal eyes and those with primary angle-closure glaucoma. For normal eyes, no correlations could be found between age and corneal thickness or axial length (over this range), while eyes with the primary angle-closure glaucoma showed a minute amount of corneal thinning. Therefore, within the limits of the measurements of these techniques, there will be no regular change in eyeball size between the ages of 30 and 85 years, so that age change of eyeball size is of no importance for primary angle-closure glaucoma.

Table IV *Summarised statistics for age* (X) v. *various parameters* (Y) *of normal eyes and eyes with primary angle-closure glaucoma*

Series of eyes	157 *normal*				118 *angle-closure glaucoma*			
Parameter (Y)	*Regression line slope*	*Analysis of variance*			*Regression line slope*	*Analysis of variance*		
		F—ratio	*P*	*Significance*		*F—ratio*	*P*	*Significance*
Central corneal thickness	+0·00022	1·17	>0·3	not	−0·00056	4·24	0·05 > P > 0·01	significant
Mean corneal radius	−0·00045	0·10	—	nil	−0·0002	0·004	—	nil
Anterior chamber depth	−0·013	47·0	<0·0005	extreme	−0·0037	3·2	0·10 > P > 0·05	not
Lens thickness	+0·015	80·4	<0·0005	extreme	+0·015	22·2	<0·001	extreme
Vitreous length	−0·0025	0·29	—	nil	−0·013	2·15	>0·10	not
Axial length	−0·00085	0·031	—	nil	−0·00041	0·0002	—	nil

Growth of the lens continues in adult life (Priestley Smith, 1883) and produces the same increase in lens thickness in both types of eyes (Table IV). Raeder (1922) and Rosengren (1931) showed that anterior chambers become steadily more shallow after the age of 25 years.

Growth of the lens leads to a shallowing of approximately 0·35 to 0·50 mm. of anterior chamber depth in 50 years (Lowe, 1969a) and this can be of significance for some cases of primary angle-closure glaucoma.

For primary angle-closure glaucoma, the regression line does not show significant shallowing of the anterior chamber with age. This is because the eyes with angle-closure glaucoma are especially selected for a range of anterior chamber depths within which primary angle-closure glaucoma is precipitated, and consequently anterior chamber depth loses correlation with age.

In normal eyes, the shallowing of anterior chamber depth occurs at a rate more than half that of the increase in lens thickness (lenses are considered to thicken evenly anteriorly and posteriorly). Although the vitreous length diminishes a little with age, this was found to lack a significant value. These features indicate a slight anterior lens displacement with age. This was first postulated by Raeder (1922) and has since received very little attention (Calmettes, Deodati, Huron, and Bechac, 1958; Weale, 1962). Measurements suggest that it is of the order of 0·2 mm. anterior lens displacement in 50 years, and as such could be considered to play an insignificant role in the genesis of primary angle-closure glaucoma (Lowe, 1970).

Discussion

In the past, the following questions have not been adequately answered:

(1) Why is the anterior lens surface sited so far anteriorly in primary angle-closure glaucoma?

(2) Is the position of the anterior lens surface determined genetically, by normal growth, or by pathological disturbances either related to or independent of the glaucomatous process?

(3) Why is hypermetropia predominant in cases of primary angle-closure glaucoma, and how do some myopes develop the disease?

The lens factors

The anterior lens surface is anteriorly sited in primary angle-closure glaucoma by two important "constitutional" factors (lens position and thickness), to which are added two factors of much less importance that are caused by advancing age (increase of lens thickness and anterior lens displacement) (Lowe, 1969a).

The "mean angle-closure glaucoma eye" has an anterior chamber that is 1·0 mm. more shallow than the mean normal eye; 0·65 mm. of this shallowing will be caused by the whole lens being sited more anteriorly and 0·35 mm. by increased lens thickness (Lowe, 1969a).

The anterior site of the lens will be almost entirely "constitutionally" determined, but a small and probably insignificant amount may be caused by the lens moving forwards with advancing age. The increased lens thickness will be mostly constitutional (and was present in the youngest cases), but a significant amount can be contributed by increased lens thickness associated with increasing age.

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No lens factor alone was found to be sufficient to cause the anterior chamber shallowing of the eyes with primary angle-closure glaucoma, but varying amounts of lens factors combined to produce the range of anterior chamber depths from 1·1 to 2·4 mm. found in the series investigated.

The cornea appears to contribute no special features in the production of shallowness of anterior chambers in primary angle-closure glaucoma (Lowe, 1969c).

Correlations

Since Steiger (1913) described a normal frequency distribution for corneal power, numerous authors have shown that all the components of refraction have a normal frequency distribution in the general population (although less for axial length than for the other components) (Sorsby, Benjamin, Davey, Sheridan, and Tanner, 1957).

In eyes of normal structure, variations in each refractive component are not randomly combined, but are co-ordinated in the interests of optimum optical function. Refractive errors are a measure of faulty correlation (Sorsby and others, 1957).

Table III shows that, in eyes with primary angle-closure glaucoma in contrast with normal eyes, the thickness and position of the lens shows no correlation with axial length. Therefore anterior chamber depth is not correlated with axial length in these eyes. Most of the shallowness of anterior chambers underlying primary angle-closure glaucoma is a result of faulty co-ordination between the lens and the eyeball wall.

The most common refractive errors are relatively small and are those that show the least deviations from the co-ordinations that produce emmetropia. Large refractive errors in otherwise normal eyes are less common because they depend upon grosser errors of ocular co-ordination. Likewise, the most frequent defects of lens co-ordination that are found in primary angle-closure glaucoma are those showing least deviation from normal co-ordinations. On the other hand, the deviations have to be sufficient to produce an anterior chamber depth within the range of risk of relative pupil block.

Because, with normal co-ordinations, the more anteriorly placed thicker lenses are found in the shorter eyes, so the eyes with primary angle-closure glaucoma with the least component inco-ordinations will have thick, anteriorly-placed lenses and shorter than average axial lengths. Owing to their axial lengths, these eyes are likely to have hypermetropic refractive errors, but the hypermetropia of the shortened axial length will be slightly reduced by the thicker and anteriorly-sited lens (refractive co-ordination).

For a thick lens to be anteriorly sited in a long eye, a much grosser disturbance of co-ordination would be necessary. Such cases do occur, but the association of myopia and primary angle-closure glaucoma will be very uncommon.

During ocular development, as well as the co-ordinations of the refractive elements, much more extensive and less easily analysed structural co-ordinations occur. The ciliary body differs in eyes with hypermetropia and myopia, and so does the origin of the iris from the ciliary body in forming the inner wall of the angle of the anterior chamber. Sugar (1941) emphasized that, in hypermetropia, the root of the iris is inserted further forwards on the antero-medial surface of the ciliary body to account for shallowness of the angle, but in myopia the root is set further back to give a relatively deep angle.

In primary angle-closure glaucoma, after iridectomy and the collapse of the iris convexity that depended upon relative pupil block, many angles remain narrow and shallow. In the iridectomy, the ciliary processes are often seen well forward, even in front of the equator of the lens (Barkan, 1954). These appearances suggest a rotation of the ciliary body, which for many years and by some authors was said to be the cause of acute congestive glaucoma.

Since the elucidation of the importance of relative pupil-block as a forerunner of acute angle-closure glaucoma, the structure of the ciliary body has tended to be overlooked; but although pupil-block is so important, shallowness of anterior chamber angles plays a part in angle-closure, especially in relation to pupil dilatation. The configuration of the ciliary body and anterior chamber angle possibly assumes more importance in the quiet, creeping angle-closure glaucoma.

The morphology of the anterior aspects of the ciliary body and the insertion of the root of the iris are probably correlated with the position and thickness of the lens.

Relative pupil-block

When anterior chamber depths are compared with age, an extremely significant correlation is found for normal eyes but not for eyes with primary angle-closure glaucoma (Table IV), but when the distance between the anterior corneal surface and posterior lens surface is compared with age, no correlation is observed for normal eyes (possibly owing to an anterior lens shift with age), but there is an extremely significant correlation for eyes with primary angle-closure glaucoma (Table V).

Table V *Statistics of age* (X) v. *distance from front of cornea to back of lens* (Y)

Eyes	*Normal*	*Angle-closure glaucoma*
Number of eyes	157	118
Regression line	Y = 7·69 + 0·0017X	Y = 6·76 + 0·011X
S.E. of regression variance	0·0018	0·0031
Due to regression variance	0·08219	1·723
About regression variance	0·08824	0·1301
F—ratio	0·930	13·239
Significance	0·50 > P > 0·70 not significant	P < 0·0005 extremely significant
Correlation coefficient "r"	+0·0772	+0·3200
Significance	not significant	P < 0·001 extremely significant

The rate of increase of lens thickness with age was found to be the same in the normal eyes and in those with angle-closure glaucoma (Table IV). Thus, in primary angle-closure glaucoma, the lens seems to grow posteriorly or to move regularly posteriorly with age, but a more satisfactory explanation is that the eyes with angle-closure glaucoma are not random samples, but form a highly selected group within certain limits of anterior chamber depth. The selecting agent is the primary angle-closure glaucoma disease which within this anterior chamber depth range develops without any correlation with age.

Primary angle-closure glaucoma depends upon relative pupil-block, which requires the anterior lens surface to be set sufficiently forward to permit the trigger mechanisms to act.

Although Tornquist (1956) stated that it was not possible to determine a "crucial threshold value below which the risk of acute glaucoma appears", nevertheless primary angle-closure glaucoma is extremely uncommon in eyes with anterior chambers deeper than 2·4 mm. The frequency of this type of glaucoma then increases as the anterior chamber depth progressively decreases to 1·8 or 1·7 mm. Shallower anterior chambers probably have an even bigger risk of pupil-block angle-closure, but they become of increasingly infrequent occurrence because of the diminishing incidence of the grosser lens inco-ordinations required to produce them.

The pupil-block angle-closure mechanism is not confined to constitutionally predisposed eyes, but is likely to occur when the anterior lens surface is displaced forwards by many different conditions; for example—by swelling or anterior subluxation of the lens, by traction of corneo-lens adhesions, by the thrust of posterior space-occupying lesions, or even by other substances (vitreous) which provide a comparable tampon. The constitutional shallow anterior chambers are almost invariably bilateral, whereas the secondarily shallowed anterior chambers are nearly always unilateral.

Comparison of means

When the means of the tabled measurements of normal eyes are compared with those of eyes with angle-closure glaucoma, highly significant differences are found (Table II); yet within the parameters there is considerable overlap for the measurements from the two groups of eyes.

In the general population, anterior chamber depth is distributed with normal Gaussian frequency (Rosengren, 1931; Stenström, 1946; Sorsby and others, 1957), and a portion of the Gaussian curve extends into the range of anterior chamber depths characteristic for primary angle-closure glaucoma. Rosengren (1931) found that, of his series of 810 normal eyes aged from 25 to 92 years, 2·3 per cent. had anterior chamber depths less than 2·0 mm.

Routine examinations of clinic patients show that shallow anterior chambers are not rare, and in practice they are much more frequently seen than cases of angle-closure glaucoma. Ocular biometry upon a small series of these patients has given results similar to those described from eyes with angle-closure glaucoma (Lowe, unpublished).

Thus, the fundamental anatomical characteristics of primary angle-closure glaucoma are not confined to eyes involved in this disease, but exist in considerably greater numbers in the general population. Most of these eyes will proceed throughout life without developing the complication of primary angle-closure glaucoma. This emphasizes the importance of the disordered physiology which is required to act upon the inco-ordinated anatomy to produce the eye disease.

The fundamental anatomical features of primary angle-closure glaucoma appear to be "constitutional" and probably determined by polygenic inheritance. Evidence for the inheritance of shallow anterior chambers was given by Tornquist (1953).

Summary

The characteristic shallow anterior chambers of primary angle-closure glaucoma are caused by inco-ordinations of structure between the lens and the eyeball. The most important lens factors are constitutional, exist in the general population, and are probably of polygenic inheritance. The constitutional lens factors are anterior lens siting and increased lens thickness, to which may be added increased lens thickness with advancing age. Combinations of various amounts of these lens factors produce shallow anterior chambers which are selected by primary angle-closure glaucoma within the range of 1·1 to 2·4 mm. of anterior chamber depth. The thick, anteriorly sited lenses can be expected to affect the ciliary body, causing its apparent rotation and shallowness of the anterior chamber angle.

These investigations formed part of Research Projects No. 13 of the Royal Victorian Eye and Ear Hospital, and No. 14 of the Ophthalmic Research Institute of Australia. Valuable clinical and technical assistance was given by Dr. Magda Horvat and the statistics were analysed by Mr. K. Shankly, M.Sc., with the computer in the biophysics section of the Department of Physiology at the University of Melbourne. My hospital colleagues kindly permitted examination of their patients and access to their records.

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Blindness due to aneurysm of anterior communicating artery

With recovery following carotid ligation

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Aneurysms of the anterior communicating artery are an uncommon cause of visual, olfactory, mental, endocrine, and sphincteric disturbance. In this paper is presented a patient with a giant anterior communicating aneurysm, causing headache, severe constriction of visual fields, and diminution of visual acuity. Transient diabetes insipidus, mental change, and urinary retention were also noted. Improvement occurred after ligation of the right common carotid artery.

Case history

A 54-year-old woman presented in July, 1965, with a 5-week history of blurred vision and transient pain in the right eye. She could just count fingers held 6 in. from the right eye and the visual acuity in the left eye was 6/36. Both optic discs appeared normal but the right pupil reacted sluggishly to light, accommodation, and convergence. Bjerrum screening showed a normal visual field for the left eye but the right eye showed complete inferior nasal quadrantic and incomplete inferior temporal quadrantic defects (Fig. 1). No other neurological abnormality was found. In particular there was no olfactory, mental, endocrine, or hypothalamic disturbance. The blood pressure was normal (150/95) and no cranial bruits were heard.

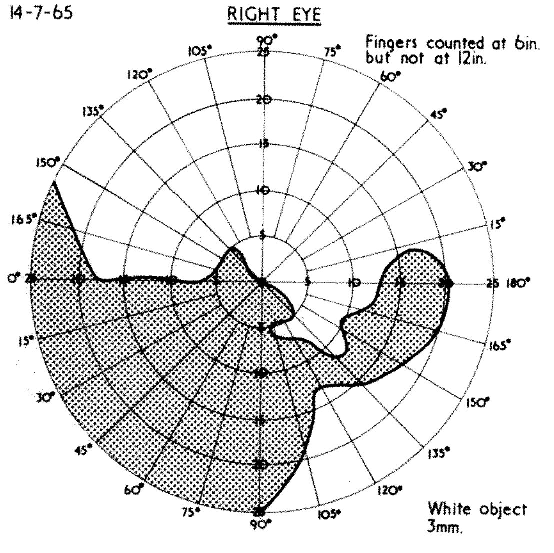

FIG. 1 *Inferior nasal and temporal quadrant defects in the right eye (July, 1965)*

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Radiographs of the skull were normal. The blood Wassermann and Kahn reactions were negative. A right carotid angiogram (Dr. G. F. Swann) showed a large aneurysm of the anterior communicating artery with good filling on cross-compression (Fig. 2). Surgery was not thought advisable at that stage.

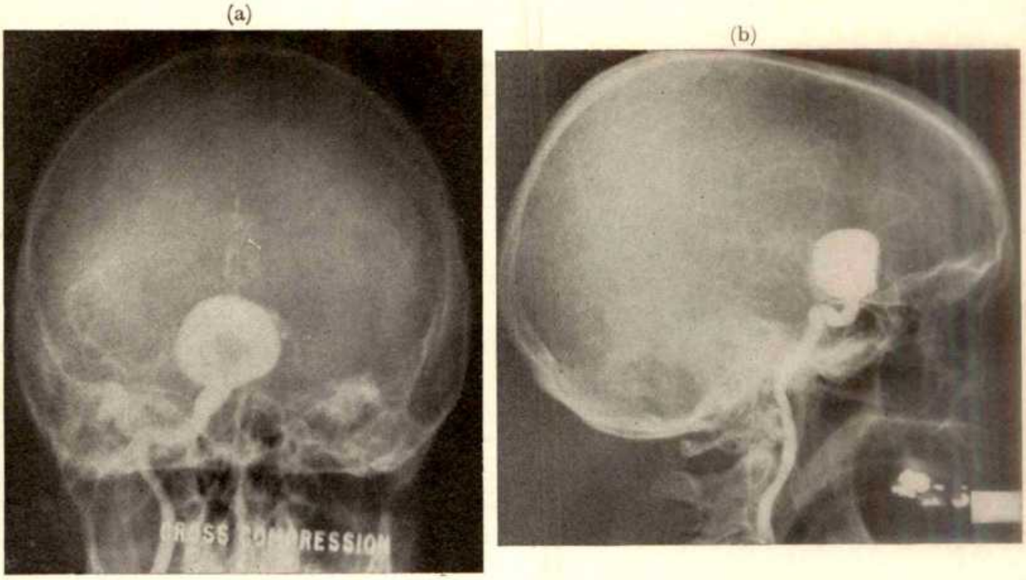
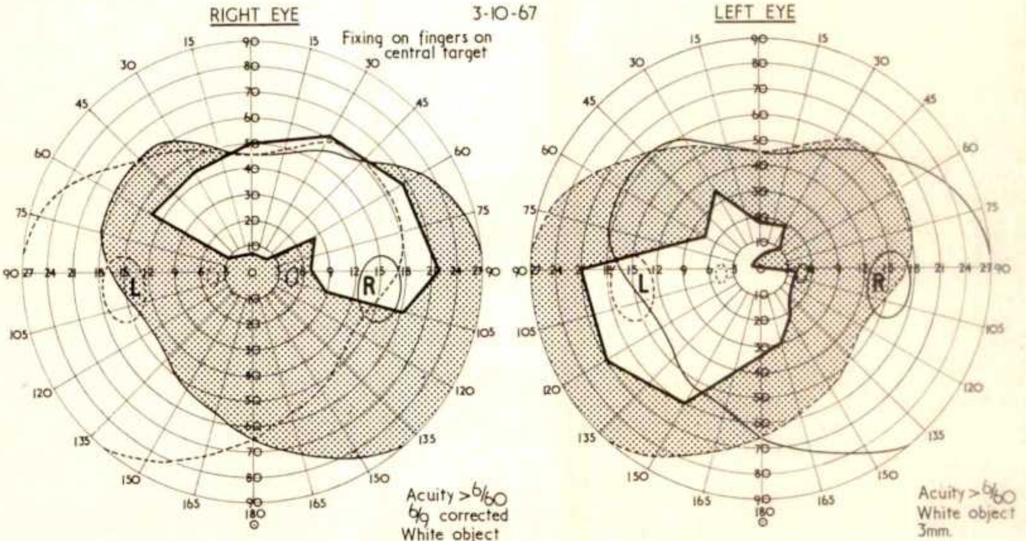


FIG. 2 *Right carotid angiogram, showing aneurysm of anterior communicating artery (July, 1965)*

September, 1967 For 3 weeks the patient had noticed pain and blurred vision in the left eye, but thought the sight of the right eye had not changed. Examination revealed optic atrophy in the right fundus with a visual acuity of less than 6/60 (6/9 corrected). The visual acuity in the left eye was also less than 6/60 and could not be improved. Considerable reduction in both visual fields had occurred (Figs 3 and 4). No further neurological deficit was found.



FIGS 3 and 4 *Considerable reduction in visual fields in both eyes (September, 1967)*

Plain skull radiographs showed asymmetry of the pituitary fossa with erosion of the posterior clinoid processes. Bilateral carotid angiography (Dr. G. F. Swann) showed that the aneurysm had considerably enlarged (6 cm. in transverse diameter compared with 4 cm. in 1965) (Fig. 5).

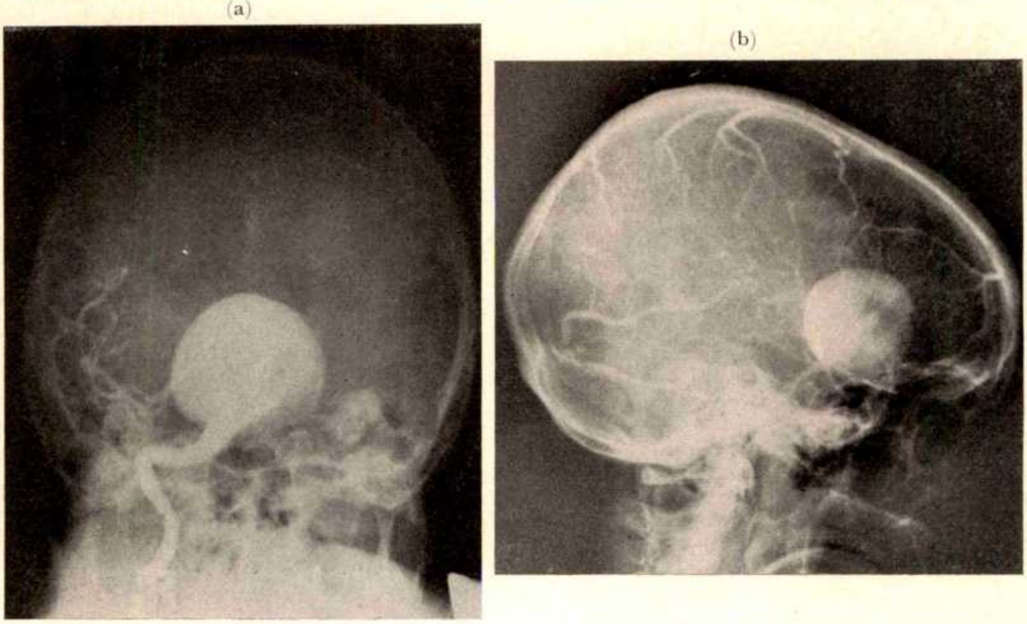


FIG. 5 *Bilateral carotid angiography, showing enlargement of aneurysm (September, 1967)*

Occlusion of the right common carotid artery for 15 min. produced no clinical change (after Matas, 1909).

Operation (October, 1967) The artery was doubly ligated on October 24, 1967 (Mr. I. R. McCaul). After operation the vision continued to deteriorate, and 3 weeks post-operatively there was no perception of light in the left eye. The right eye showed a worsening field defect (Fig. 6). The patient's name was placed on the Register of Blind Persons.

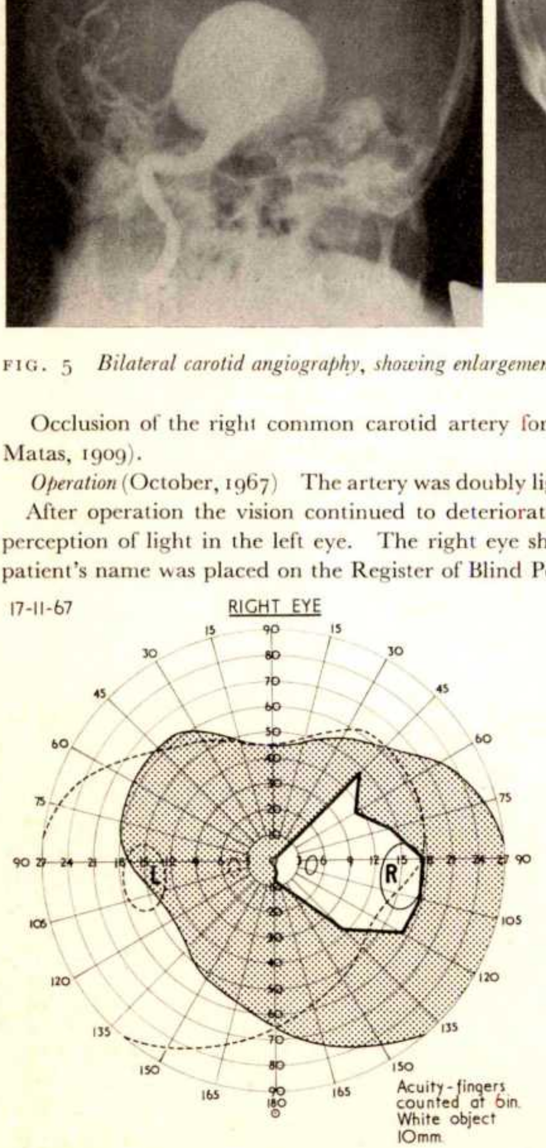


FIG. 6 *Deterioration in visual field in right eye (November, 1967)*

Two weeks after the operation, thirst and polyuria developed with transient urinary retention. Diabetes insipidus was confirmed by fluid input and output studies before and after intramuscular pitressin. There was a good clinical response to Di-Sipidin snuff. During this period considerable mental change was noted. The patient became prone to attacks of rage but these eventually subsided spontaneously. No evidence of anterior pituitary lobe dysfunction was found (see Table).

Table *Tests of anterior pituitary lobe function (all results were within normal limits)*

1. Serum cholesterol 235 mg./100 ml.

2. Serum protein-bound iodine 6·6 μg./100 ml. (repeated 6·0 μg./100 ml.)

3. Growth hormone radio-immune assay 100 i.u./day (repeated 24 i.u./day)

4. Vasopressin response

Plasma cortisol (μg./100 ml.) (1) 24·5
(2) 20·0
(3) 18·0

5. Synacthen response

Plasma cortisol (μg./100 ml.) (1) 14·5
(2) 38·0

6. Metyropone response

Urinary 17-OH corticosteroid output (mg./24 hrs)	Total volume (ml.)
(1) 7·5	3030
(2) 11·2	3910
(3) 48·8	3600
(4) 102·4	3400
(5) 58·4	2800

7. Insulin tolerance Blood glucose (mg./100 ml.)

Control	*Insulin*					
	+15 min.	+30	+45	+60	+75	+90
63	60	16	22	41	47	69

8. Insulin/cortisol response Plasma cortisol (μg./100 ml.)

Control	*Insulin*		
	+30 min.	+60	+90
18·5	19·0	48·5	48·5

9. Insulin/growth hormone response Plasma growth hormone (μg./ml.)

Control	*Insulin*			
	+30 min.	+60	+90	+120
5	7	35	12	6

January, 1968 *i.e.* 3 months after the operation, the patient's vision and headache suddenly began to improve; about the same time, the diabetes insipidus remitted and has not recurred. No further mental change has been noted.

October, 1968 Visual improvement has continued and in October, 1968, the acuity was 6/5 (corrected) in the left eye and fingers held at 12 in. could be counted with the right eye. The visual field of the left eye had become full and that of the right eye had considerably increased, although there was still a nasal hemianopia (Fig. 7). The patient's name was removed from the Register of Blind Persons. The atrophic appearance of the right optic disc was unchanged and the right pupillary reactions remained sluggish.

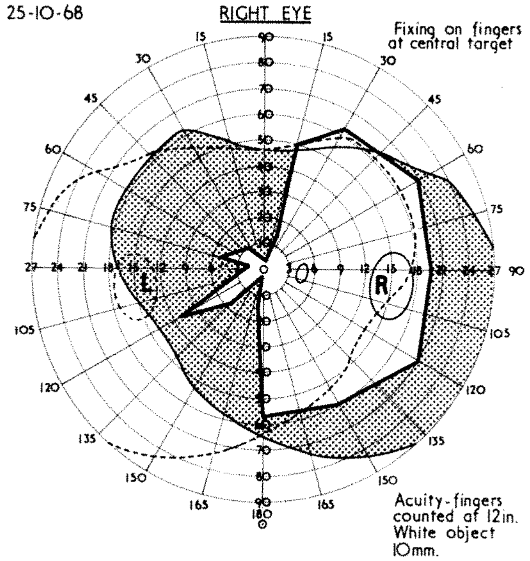

25-10-68
RIGHT EYE
Fixing on fingers at central target
15
30
45
60
75
90
105
120
135
150
165
180
L
R
Acuity-fingers counted at 12in. White object 10mm.

FIG. 7 *Improvement in visual fields was noted in October, 1968, but there was still nasal hemianopia in the right eye*

Discussion

Norlén and Barnum (1953) have estimated that there is a 1 per cent. incidence of intracranial aneurysm in the general population. Of these, 20 to 25 per cent. affect the anterior communicating artery. Intracranial aneurysms frequently present with headache, subarachnoid haemorrhage, or epilepsy. They may cause sudden or gradual symptoms by compressing the brain stem, cerebral hemispheres, or cranial nerves. Aneurysms of the anterior cerebral or anterior communicating arteries may also cause mental, olfactory, sphincteric, hypothalamic, or endocrine disturbances, although these are unusual (Jefferson, 1937; Meadows, 1951). Symptoms due to pressure by an anterior communicating aneurysm on the optic nerves or chiasm are also uncommon. Jefferson (1937) reviewed 66 cases of amblyopia and field defect caused by intracranial aneurysms at various sites and described twelve of his own. Six of his cases showed optic nerve or chiasmal compression although the anterior communicating artery was not the site of the lesion. Each presented with a history similar to that described above, *viz.* headache, acute diminution in visual acuity, and field defects. Similar cases were described by Dailey, Holloway, Murto, and Schlezinger (1964) and Cullen, Haining, and Crombie (1966).

It seems clear that direct compression of the optic nerve by the aneurysm is not the sole cause of the loss of vision. Distortion of the optic nerve at the foramen plays an important part as does interference with the blood supply of the proximal optic nerve or the chiasma. The latter point was brought out by Richardson and Rose (1965), who described a patient who died from pituitary apoplexy. Symmetrical small haemorrhages were found in the optic nerve at the point where they were crossed by the anterior communicating artery.

The diagnosis is usually confirmed, but not invariably if clotting has occurred, by bilateral carotid arteriography. This procedure may not only confirm the size, shape, and position of the lesion, or show up some other unsuspected vascular anomaly, but it is also of importance, when planning surgery, in determining to what extent each carotid system supplies the aneurysm (Norlén and Barnum, 1953). This is especially important when carotid ligation is contemplated. The Matas test is also of value in this connexion. Plain skull radiography may show erosion of the dorsum sellae or calcification in the wall of the aneurysms. The testing of pituitary function may reveal an unsuspected latent hypopituitarism necessitating corticosteroid cover for operation. In the patient described, symptoms of diabetes insipidus developed after surgery. Anterior lobe function was found to be normal but ideally this should have been assessed preoperatively (Nieman, Landon, and Wynn, 1967).

Recently reported series deal primarily with surgery after subarachnoid haemorrhage (Robertson, 1949; Rogers, 1949; Elvidge and Feindel, 1950; Falconer, 1951; Poppen, 1951; Wechsler, Gross, and Cohen, 1951; Bassett, List, and Lemmen, 1952; Black and German, 1953; Brackett, 1953; Logue, 1956). Little or no mention is made of the treatment of visual disturbances *per se* but no visual deterioration was reported after carotid ligation. Most neurosurgeons seem to favour the direct approach for anterior communicating aneurysm with a view to clipping the neck of the lesion. There is a risk of venous thrombosis but frontal lobe infarction is more likely after carotid ligation, except when the aneurysm fills equally well from both sides (Poppen, 1951).

There remains a small group of cases such as that described, with a supraclinoid aneurysm adjudged too large for direct surgery. When such lesions are causing severe pain or impairment of vision, carotid ligation would seem to be indicated (Meadows, 1951; Norlén and Olivecrona, 1953). There are a few reports of patients who, as in the case described, showed considerable improvement after such treatment (Birley and Trotter, 1928; Jefferson, 1937; Krayenbühl, 1946; Höök and Norlén, 1964; Shealy and Kaufman, 1965). Ligation of the common, rather than of the internal carotid, artery seems less likely to produce a hemiparesis. Occasionally spontaneous improvement may occur, presumably by clot formation (Conway, 1926). It is well recognized that symptoms due to chiasmal compression by pituitary tumours may spontaneously improve, probably after infarction.

The mechanism of improvement after carotid ligation is obscure. Reduction of the pressure in the aneurysm, with or without subsequent thrombosis, presumably allows partial recovery of the compressed structures. Oedema is possibly lessened and arterial or venous channels may re-open, especially if surgery is performed sufficiently early after an exacerbation in symptomatology. A reduction in pressure may also possibly cause a slight shift in position of the lesion. The earlier the pressure is reduced the more neurological recovery may be expected.

We acknowledge with thanks the help of Mr. E. J. Arnott, Dr. K. D. Bagshawe, Mr. D. A. Langley, Mr. I. R. McCaul, and Dr. G. F. Swann, in the management of this patient.

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Behaviour of an iris model and the pupil block hypothesis

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While the immediate cause of primary acute glaucoma is known to be obstruction of the anterior chamber angle by peripheral iris tissue, the mechanism leading to angle closure remains uncertain.

One hypothesis which has been proposed to explain the phenomenon involves the concept of relative pupil block. It is suggested that the iris, stretched across the lens, obstructs the flow of aqueous from the posterior to the anterior chambers. A pressure gradient between the two chambers is necessary for flow to continue, and the resistance to flow is known as relative pupil block. If the pupil block increases a greater pressure is required to force aqueous between the apposing surfaces of the lens and iris, causing the peripheral iris to bow forwards and touch the angle structures. The drainage meshwork is obstructed, the intraocular pressure rises rapidly, and acute congestive glaucoma may follow (Chandler, 1952; Barkan, 1954).

Theoretical analyses of the pupil block mechanism have been attempted, for example, by Lowe (1966) and by Mapstone (1968). However, the physical basis of the theory remains untested. This paper reports preliminary observations on the behaviour of an annular elastic membrane stretched across a ball, and the findings are related to the pupil block hypothesis.

Method

A model was built using a plastic jar, with an annular elastic membrane stretched across its top to represent the iris (Fig. 1, overleaf). The central aperture of the membrane was blocked by a ball to represent the lens. Air blown into the jar from below escaped through the gap between the membrane and the ball causing the membrane to bow forward, and the profile of the membrane was plotted on graph paper. In this way the effect of changes in air flow, in membrane tension, in membrane aperture, and in ball position was studied.

The jar, which was 13 cm. high and 11 cm. wide, was covered by a lid held on by four springs. A hole of 10 cm. diameter was cut in the lid, and an annular elastic membrane was stretched across the hole and held in place by a plastic ring clamped under four nuts. The membrane was prepared from surgical gloves and the hole in its centre, representing the pupil, was cut to a measured diameter while the membrane was slack. When the membrane was stretched in position the change in diameter of the central hole gave an indication of the tension in the membrane.

A threaded brass rod was fixed to the base of the jar and projected through the centre of the hole in the lid. A ball 6·4 cm. in diameter, with a threaded central bush, was screwed down the rod into the membrane opening, so that its position with relation to the plane of the lid could be varied.

Air was blown from an electrically driven pump through an anaesthetic flow-meter and into the jar. The pressure in the jar was measured using a water-filled U-tube manometer.

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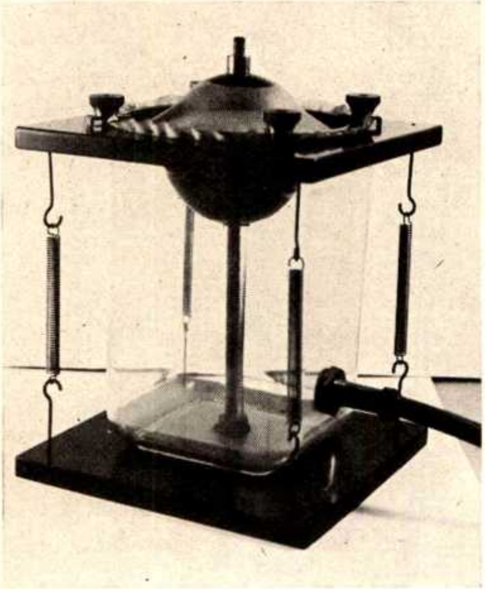

FIG. 1 *The model*

Changes in the membrane shape were plotted using a modified jig-gauge.

In each experiment the following observations and measurements were made:

(1) The diameter of the aperture in the membrane.
(2) The position of the ball in relation to the plane of the lid.
(3) The air flow through the model.
(4) The pressure behind the membrane.
(5) The resulting profile of the membrane.

Results

(A) EFFECT OF CHANGES IN AIR FLOW UPON MEMBRANE SHAPE

In this experiment the membrane was set so that a hole which was 1 cm. initially became 2 cm. in diameter when stretched over the ball. The ball was adjusted to project 2·5 cm. above the plane of the lid.

Membrane shape was recorded at air flows of 0, 100, 200, 300, 400, 500, 750, 1,000, and 1,500 ml./min. A selection of the results is shown in Fig. 2 (opposite).

At zero flow the membrane adopted a shallow S-shaped curve, forming a hollow between the point of contact with the ball and the periphery (Fig. 2*a*). As the air flow increased that part of the membrane which was not in contact with the ball began to move forwards, flattening the S-shaped curve, and simultaneously the outer part of the area of contact began to lift off the ball (Figs 2*b*, *c*, and *d*).

Maximum forward bowing was reached at an air flow of 500 ml./min., when only the edge of the central aperture touched the ball (Fig. 2*d*). Further increase of air flow did not increase the forward bowing of the membrane, which at this stage formed a segment of a sphere.

Forward bowing of the membrane was associated with an increase in pressure behind the membrane (Table I). The diameter of the central aperture in the membrane did not change by a measurable amount between the least and greatest air flows.

Table I *Results from first experiment, using single membrane with ball projecting 2·5 cm. above plane of lid*

Air flow (*ml./min.*)	*Pressure* (*cm. water*)	*Resistance* (*cm./l./min.*)	*Contact area** *between membrane and ball* (□*cm./π*)
0	0	0	6·38
100	5·7	57·0	5·08
200	10·6	53·0	3·46
300	15·7	52·3	1·59
400	18·0	45·0	0·98
500	18·5	37·0	0·58
750	18·8	25·0	0
1,000	18.9	18·9	0
1,500	19·0	12·7	0

* These figures are an approximation, being calculated for flat and not spherical surfaces

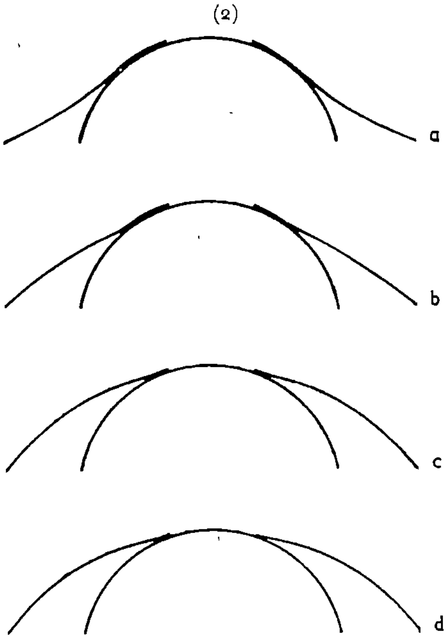

FIG. 2 *Profiles of a single-thickness membrane at air flows of* (a) 0, (b) 200, (c) 300, (d) 500 *ml./min. Ball set to project* 2·5 *cm. above plane of lid*

(B) EFFECT OF CHANGING MEMBRANE TENSION

In the second series of experiments two thicknesses of membrane were cut, each with a central hole of 1 cm. diameter, and the doubled membrane was stretched over the ball until the central aperture was 2 cm. in diameter. By doubling the thickness of the membrane and stretching the doubled membrane to the same degree as the single membrane the effect of doubling the membrane tension was achieved. In every other way the conditions of the experiment were identical with those described for the single membrane.

A selection of the results is shown in Fig. 3 (overleaf). The air flows in Figs 3*a*, *b*, *c*, and *d* were the same as those in Figs 2*a*, *b*, *c* and *d*.

No difference could be detected between any of the curves when Figs 2 and 3 were compared, although calculation of contact areas from the measured contact arcs suggested that the contact area of the doubled membrane was greater than that of the single membrane at the same air flow (Tables I and II). Maximum forward bowing occurred at 500 ml./min. as for the single membrane, and again the central aperture diameter did not change by a measurable amount. The increases of pressure corresponding to increases of flow were greater than for the single membrane (Table II overleaf).

(C) EFFECT OF CHANGING MEMBRANE APERTURE

Membrane profiles were plotted with different membrane apertures when the ball projected 2·5 cm. above the plane of the lid and the air flow was 1,500 ml./min.

Apertures were cut in the slack membrane at diameters of 1, 2, 3, 4, and 5 cm., and the aperture diameters when the membrane was stretched over the ball are shown in Table III (overleaf).

A selection of the resulting profiles is shown in Fig. 4*a*, *b*, *c*, *d* (overleaf). A decrease in the membrane aperture led to an increase in forward bowing of the membrane.

Table II *Results from second experiment, using double membrane with ball projecting 2·5 cm. above plane of lid*

Air flow (*ml./min.*)	*Pressure* (*cm. water*)	*Resistance* (*cm./l./min.*)	*Contact area* between membrane and ball* (□*cm./π*)
0	0	0	6·38
100	8·3	83 5	5·32
200	16·3	81·5	3 90
300	24·4	81·3	2·28
400	30·6	76 5	1·28
500	34·0	68·0	0·45
750	36·8	49·0	0
1,000	37·7	37·7	0
1,500	38·3	25·5	0

* These figures are an approximation, being calculated for flat and not spherical surfaces

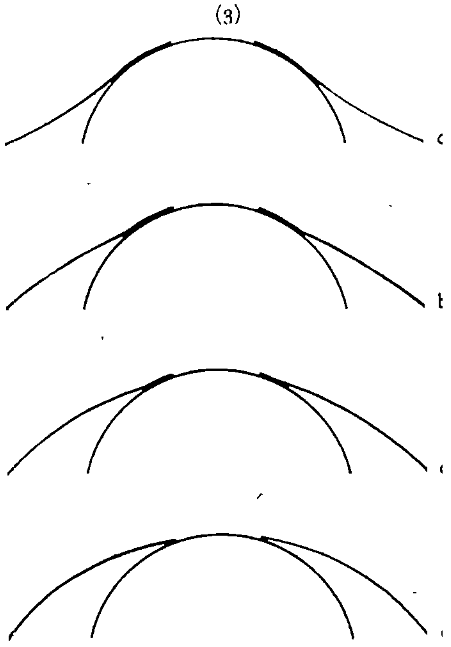

FIG. 3 *Profiles of a double-thickness membrane at air flows of* (a) 0, (b) 200, (c) 300, (d) 500 *ml./min. Ball set to project* 2·5 *cm. above plane of lid*

Table III *Diameter of aperture in membrane when stretched over ball, compared with aperture in slack membrane, in Experiment C*

Aperture (*cm. diameter*)							
	Slack	0·9	2·0	3·0	4·0	5 0	6·0
	Stretched	2·1	3·2	4·1	5·0	5 6	6·3

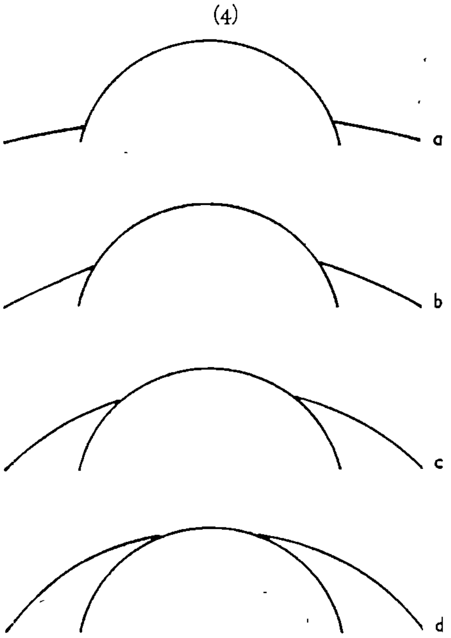

FIG. 4 *Profiles of single-thickness membranes with different sized apertures as shown in Table III. Ball set to project* 2·5 *cm. above plane of lid. Air flow* 1,500 *ml./min.*

(D) EFFECT OF CHANGING THE POSITION OF THE BALL

Membrane profiles were plotted with an air flow of 200 ml./min. when the ball projected above the plane of the lid by 0·6, 1·0, 1·5, 1·75, 2·0, 2·25, and 2·5 cm.

The aperture in the membrane which was cut to a diameter of 1·0 cm. before stretching, increased by a small amount at each forward movement of the ball, showing that the tension in the membrane was changed by this procedure (Figs 5*a*, *b*, *c*, *d*).

Forward movement of the ball at constant air flow resulted in an increased forward bowing of the membrane. A selection of the resulting profiles is shown in Fig. 5. The pressure behind the membrane also increased as the ball was moved forward (Table IV).

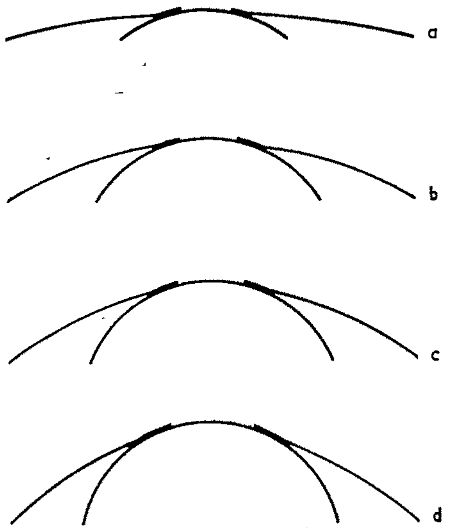

FIG. 5 *Profiles of single-thickness membrane at an air flow of* 200 *ml./min., the ball being set to project* (a) 0·6 *cm.*, (b) 1·5 *cm.*, (c) 2·0 *cm.*, (d) 2·5 *cm. above plane of lid*

Table IV *Results from fourth experiment to study effects of changing position of ball, with air flow 200 ml./min.*

Ball projection above plane of lid (*cm.*)	0·6	1·0	1·5	1·75	2·0	2·25	2·5
Pressure behind membrane (*cm. water*)	2·0	4·6	9·6	11·0	11·9	12·5	13·0
Resistance to flow (*cm. water/l./min.*)	10	23	48	55	59	63	65

Discussion

(A) THE ANALOGY

Interpretation of the results of these experiments depends on an analogy between the iris and a stretched elastic annular membrane. This analogy may be supported in two ways:

(*1*) The analogy appears to be implicit in discussions of the pupil block mechanism, although it is not directly stated. The behaviour of a physiological system depending on mechanics for its interpretation should be imitable by a mechanical model.

(*2*) It is not likely that a muscle-controlled membrane would behave in a more than elastic manner, that is, that it would decrease in tonus as it was put under tension. The reverse is more likely, that it would become more rigid as its tension rose and in this case the succeeding arguments would still apply.

(B) THE PUPIL BLOCK HYPOTHESIS

The hypothesis proposes that an increase in relative pupil block leads to an increase in iris bombé. It is considered that the increased block may be brought about in one or more of three ways; by an increase in tension in the iris; by a mid-dilated position of the pupil; or by a forward movement of the lens.

(1) *Changes in iris tension*

Several authors have suggested that an increase in iris tension, caused by the extreme meiosis of drugs or by co-contraction of the sphincter and dilator muscles, would lead to an increased pupil block and hence an increase in iris bombé (Chandler, 1952; Becker and Shaffer, 1965; Lowe, 1967; Pollack, 1967; Mapstone, 1968; Boyd, 1968).

In the model, doubling of the membrane tension increased the resistance to air flow between the membrane and the ball—the equivalent of pupil block in the eye (compare Tables I and II). Despite this increase in resistance, the shape of the membrane was unchanged at comparable air flows, and the model gave no support to the hypothesis. The difference in the computed contact areas between the single and double membranes is probably due to experimental error but, even if the difference is real, the hypothesis remains unsupported.

How is this to be explained? In discussion of the mechanism of acute glaucoma, it is usually assumed that the rate of aqueous secretion is constant. Two variables then remain relating to flow through the pupil; the pressure differential between posterior and anterior chambers; and the resistance to flow. If both the pressure differential and the resistance to flow depend on the tension in the iris, changes in iris tension should have a similar effect on both parameters.

In each of the first two series of experiments described here, as the air flow increased and the membrane moved forward into the "bombé" position, its central aperture did not increase in diameter. Since the aperture size gives an indication of the tension in the membrane, it is apparent that the tension scarcely changed as the membrane moved forward, and changing tension could not explain the rising pressure in the space behind the membrane.

However, when the pressure behind the membrane was compared with the area of membrane not in contact with the ball—the "free" membrane exposed to the air in the posterior space—an approximately linear relationship was found, with the slope of the line for the doubled membrane steeper than that for the single membrane (Fig. 6).

Evidently two factors determine the pressure behind the membrane: the tension in the membrane (which did not change with changing flow but was doubled by doubling the membrane) and the area of membrane not in contact with the ball. At any given flow, doubling the membrane caused an increase in pressure without a change in contact area.

Similarly the resistance to flow must depend on the pressure between the membrane and the ball, and on the area of contact between the two. The contact pressure was not measured in these experiments, but it is likely that it too was dependent on the membrane tension. If this is so then an increased tension in the membrane could lead to an increased resistance to flow without a change of contact area.

Since the membrane curvature did not change when the membrane tension was doubled, the pressure behind the membrane must have risen in proportion to the resistance to flow.

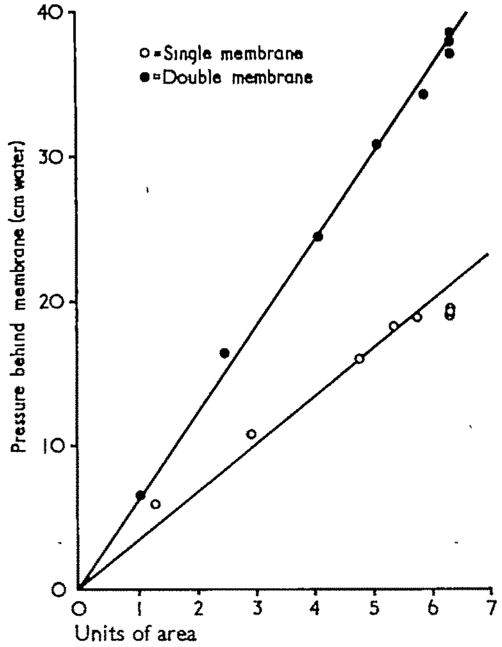

FIG. 6. *Relationship between pressure behind membrane and area of membrane exposed to posterior space*

(2) *Diameter of the pupil*

It is widely accepted that a position of mid-dilation of the pupil in a pre-disposed eye carries an especial risk of precipitating acute glaucoma, and this has been assumed to be because pupil block is still a significant factor while the periphery of the iris is now relatively lax (for example, see Chandler, 1952; Becker and Shaffer, 1965).

There was no evidence in the behaviour of the model to support this theory. As the membrane aperture was increased the area of contact between the membrane and the ball decreased, the resistance to flow decreased, and the membrane bowed less.

In this experiment it was not possible to keep the tension constant while changing the aperture, because there was no direct method of regulating the tension. However, it has already been shown that, at a given flow, the membrane curvature was independent of its tension, so that this is not likely to lead to a significant error.

If a mid-dilated position of the pupil is indeed especially dangerous, it is probably for reasons other than its effect on pupil block, a possibility discussed in Section C below.

(3) *Forward movement of the lens*

Barkan (1954) proposed that a forward movement of the lens caused by accumulation of fluid in the posterior compartment of the eye might be the cause of increased pupil block leading to acute glaucoma. This view is supported by the studies of Christensen and Irvine (1966), Bleeker (1963), and Bleeker, van Haeringen, and Glasius (1963), but is opposed by those of Rosengren (1950).

Moving the ball forward in the model produced a progressive increase in resistance to air flow (Table IV) which was associated with a progressive increase in the forward bowing of the peripheral part of the membrane. Thus Barkan's hypothesis is supported by the behaviour of the model. Further studies of the changes in anterior chamber depth associated with acute glaucoma would be of value.

(C) OTHER ASPECTS OF THE BEHAVIOUR OF THE MODEL

The model has been shown to support only one of the three mechanisms proposed for the means by which increased pupil block may lead to acute glaucoma. It also suggests another factor which may be important in the genesis of the disease.

In the experiments described here, the ball was fixed to the centre rod so that the forces acting on the ball could not be assessed. However, it is probable that two opposing forces are involved. The stretched membrane tended to force the ball back into the jar, and this force was greatest when air flow was nil—a condition comparable to that of the eye after peripheral iridectomy. Increasing membrane aperture would decrease this force, and increased membrane tension would increase it.

There is also a force tending to displace the ball forwards, pushing it through the membrane aperture. This phenomenon was studied by Koster (1895) who constructed a model to demonstrate how the lens acted as a valve in the pupil aperture. He showed that an unsuspended ball could be made to block the central aperture in an annular elastic membrane by applying a large pressure differential across the membrane. The ball would stay in that position as the pressure differential was reduced and would not fall away from the aperture until the pressure differential was only that of a few cm. of water. The same observation was made in a rather different form by Moses (1963).

In a stable state, any difference between these forces must be balanced by the suspensory system of the ball, in this case the threaded rod.

In the eye the iris corresponds to the elastic membrane, the pressure differential between posterior and anterior chambers to the pressure behind the membrane, and the zonular tension to the screw thread on the ball. Accommodation, usually associated with meiosis, would slacken the zonule. If the pupil dilated at the same time, those forces holding the lens back would be reduced, and forward displacement of the lens could occur. It is suggested that the balance between these forces may govern the position of the lens, and that a particular form of imbalance may lead to its forward displacement in acute glaucoma.

A study of the relationship between these forces will be reported in a succeeding paper.

Summary

The pupil block hypothesis relating to the genesis of acute glaucoma was tested on a model. The apparatus was relatively simple, but the results were clearly defined. Only the theory that forward movement of the lens might precipitate acute glaucoma could be supported. Implications for further studies are discussed.

Our thanks are due to Mr. Howells of Shandon-Elliott Ltd., Liverpool, who made the model, and to Mr. T. D. H. Gray for his helpful discussion and criticism.

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Brit. J. Ophthal. (1970) 54, 186

Mechanisms of presentation of carotico-cavernous fistulae

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The clinical features of carotico-cavernous fistulae are too well known for detailed description to be necessary. The proptosis, chemosis, venous engorgement in and around the orbit, oculomotor palsy, pulsation of the globe, and the subjective and objective bruit over the orbit and forehead are familiar to all. It is perhaps not always appreciated that the bruit may, on occasions, precede the appearance of the other features by weeks or even months. There are, however, several modes of clinical presentation, and a number of different aetiological processes responsible. The lesion may present as the conventional unilateral carotico-cavernous fistula; the bilateral fistula; the contralateral fistula, in which the pulsating exophthalmos is on the side opposite to the actual fistula; or the alternating fistula. This has been written in these words advisedly, because there is a tendency to accept such expressions too readily and too literally without giving enough thought to their meaning. For instance, does bilateral pulsating exophthalmos mean that the patient has two symmetrical carotico-cavernous fistulae? Or does the alternation of ocular symptoms mean that one fistula has healed but by coincidence the same patient has developed another on the opposite side? It is because this must very rarely be the case that this paper has been written, to consider the mechanism by which clinical presentations of different types comes about, and also to describe two unfamiliar aetiological processes.

Anatomical considerations (Fig. 1*a*, opposite)

The cavernous sinuses lie lateral to the pituitary fossa between two layers of dura. They connect anteriorly with the superior ophthalmic veins, and through these with the supraorbital, angular, and inferior orbital veins. Posteriorly they are connected to the superior petrosal sinuses, and the inferior petrosal sinuses, and through the latter to the jugular veins. They are not isolated structures, however, but are joined together by the intercavernous sinuses, anterior and posterior, before and behind the pituitary fossa, and also through the basal venous plexus lying on the clivus, and other less important communications. The degree of patency and the relative importance of these connections varies. The sinuses themselves are not just flaccid containers of blood, but are named from the fibrous trabeculations which traverse them giving the appearance of cavernous tissue. They are the only places in the body where a major artery lies bathed in venous blood.

When considering the mechanism of carotico-cavernous fistulae, the important structures involved are the superior ophthalmic veins and the intercavernous sinuses, particularly the anterior. Their anatomical relationships vary, as does the relationship of the carotid artery to them.

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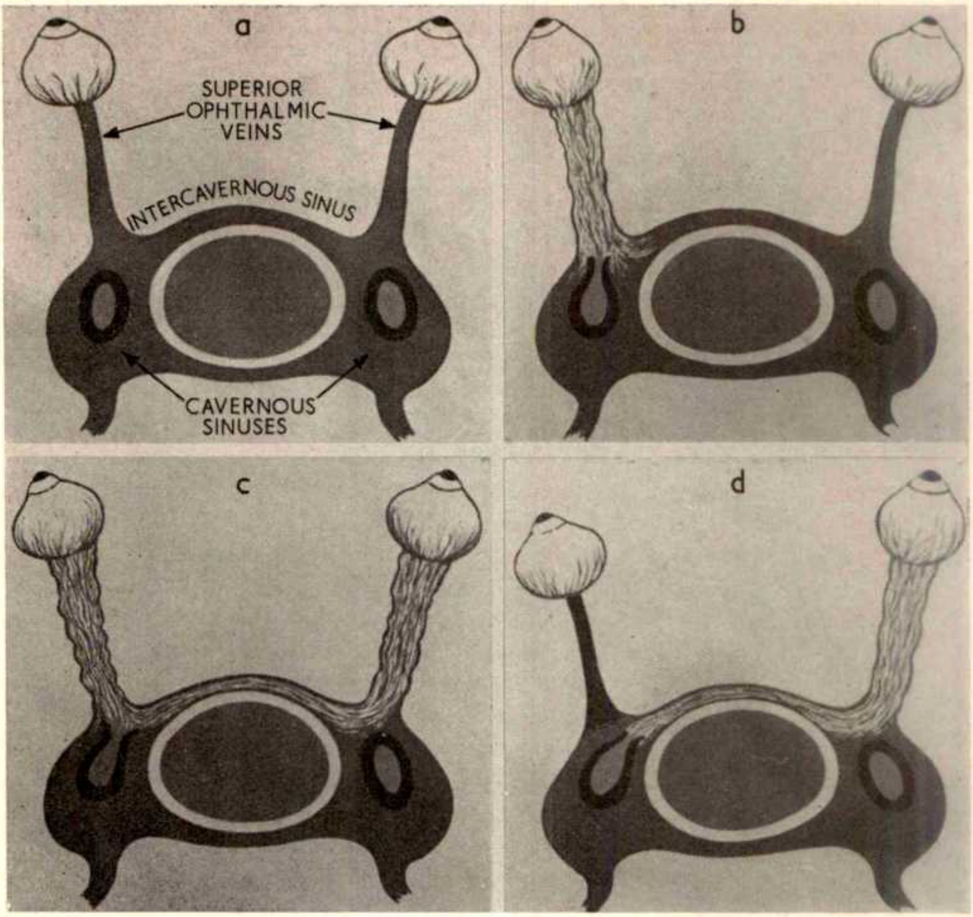

FIG. 1 *Diagrammatic representation of cavernous sinus and connecting veins*

(*a*) normal
(*b*) ipsilateral carotico-cavernous fistula
(*c*) arterial blood crossing by the intercavernous sinus gives impression of bilateral fistulæ
(*d*) ipsilateral ophthalmic vein thrombosed but intercavernous sinus patent allowing contralateral syndrome to develop.

Clinical material

The material for this study comes from a series of eleven consecutive cases of carotico-cavernous fistulae, ten of which were female, one of which was "bilateral", one contralateral, and three "alternating". All were non-traumatic in origin.

Aetiological factors

According to Walsh (1957), trauma is responsible for 75 per cent. of all cases and men are most frequently affected. In the present series, however, the chief cause of the condition is the rupture of a hypertensive atherosclerotic internal carotid artery, or of a pre-existing intracavernous aneurysm, or a combination of aneurysm, hypertension, and atheroma. Women predominate, and most of them are elderly (*e.g.* Case 1). Spontaneous fistulæ may on rare occasions occur in younger patients, however, in which neither trauma nor aneurysm play any part, and two of these unusual mechanisms are mentioned later in this paper.

Mechanism of production of clinical symptoms

Fig. 1 (*b–d*) is intended to illustrate in diagrammatic fashion the principal events which occur. When rupture occurs, arterial blood escapes from the carotid artery, enters the sinus, tracks through the trabeculae (which may delay the development of the full clinical picture), and then enters the superior ophthalmic vein (Fig. 1*b*), which becomes engorged, enlarged, and tortuous. These changes are passed forwards to the supraorbital, angular, and inferior ophthalmic veins, and arteriography will, in the lateral view, show the dye escaping into the sinus and along the distended superior ophthalmic veins to the orbit (Fig. 2). This is the mechanism of the conventional unilateral fistula with ipsilateral pulsating exophthalmos. It depends upon the superior ophthalmic vein being patent, and the intercavernous sinus being relatively unimportant.

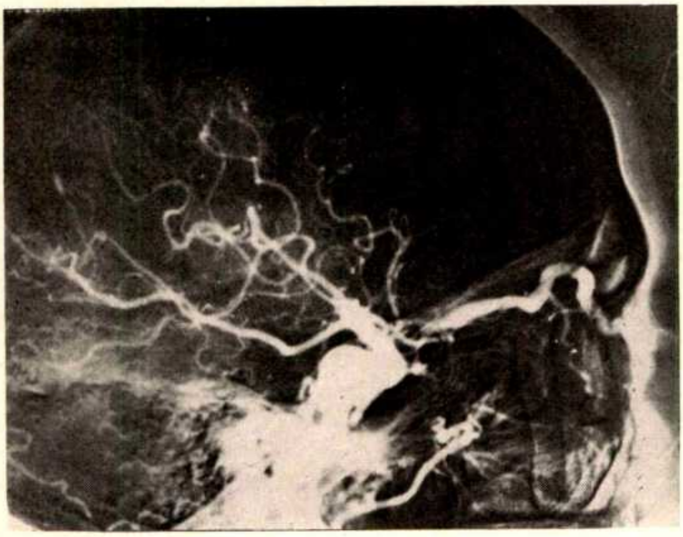

FIG. 2 *Internal carotid arteriogram (subtraction technique) showing dye entering cavernous sinus and passing along dilated superior ophthalmic vein to the orbit*

THE "BILATERAL" FISTULA (Fig. 1*c*)

If both superior ophthalmic veins are patent and in the normal position, and if the intercavernous sinus is patent, or becomes so as a result of the pressure of arterial blood in the cavernous sinus, this blood can not only pass into the superior ophthalmic vein on the side of the fistula, but can also pass across the mid-line and enter the other sinus and the other superior ophthalmic vein, thus causing bilateral pulsating exophthalmos and bruit. There is however still only one fistula, which is a point of great importance, for if this can be demonstrated arteriographically only one carotid artery need be sacrificed for both eyes to be cured.

THE CONTRALATERAL FISTULA (Fig. 1*d*)

If the superior ophthalmic vein on the side of the fistula is an unimportant structure in that particular patient, or has an unusual mode of communication, or becomes thrombosed by damage to its walls from the rush into it of arterial blood; and if the intercavernous sinus is patent or becomes so, the arterial blood can track across to the other side, entering the other superior ophthalmic vein, and so cause unilateral pulsating exophthalmos on the side opposite to the fistula. That this is not merely hypothetical was shown by Dandy and Follis (1941); there have been others in the literature, and the following patient from this series illustrated the point very clearly.

Case 1

A woman aged 58 suddenly developed a sensation of something having snapped inside her head. For 48 hours she had severe headache and developed a pulsating noise inside the head. Over the next 6 months a right-sided unilateral pulsating exophthalmos gradually became apparent with a loudly audible systolic bruit. However, when the right carotid arteriogram was carried out by Dr. Philip Moxon, no abnormality was seen. The procedure was repeated on the left side, and here it was clearly demonstrated that there was a left-sided carotico-cavernous fistula, and the dye could be seen to be tracking through the anterior intercavernous sinus to the right side, and along the right superior ophthalmic vein to the orbit. The ipsilateral ophthalmic vein did not appear to be patent. Immediately after arteriography all the symptoms ceased and all the physical signs subsided. A very careful repetition of the left carotid arteriogram was then carried out and this showed that, whereas the dye still escaped from the artery into the left cavernous sinus, the intercavernous connection had become occluded at its mid-point. This patient has remained perfectly well for over 5 years.

THE "ALTERNATING" FISTULA

If, after a conventional carotico-cavernous fistula syndrome has developed, the superior ophthalmic vein thromboses, the symptoms will settle down. It has been seen, however, in Case 1 that the fistula may remain open, and this may cause the intercavernous sinus to open up gradually, until finally arterial blood is allowed to enter the contralateral superior ophthalmic vein (Fig. 1*d*), so that the pulsating exophthalmos will re-appear, but on the opposite side. It is still only the one fistula which is present and which may require treatment.

Much of what has been said may be hypothesis, but it is clearly proven in Case 1, and it seems so much more likely that a sequence of events of this type may take place than that identical fistulae should develop coincidentally in the two carotid arteries at the same or different times.

Some additional aspects of aetiology

The commonest causes of non-traumatic carotico-cavernous fistulae have been mentioned earlier, but in the younger, non-atheromatous, normotensive patient, there must be some unusual defect in the wall of the carotid artery. The type of intracavernous aneurysm which affects the older patients is uncommon in the young, and haemorrhagic disorders rarely cause such symptoms. There may occasionally, however, exist a hereditary fragility of the vessel wall, or the vessel may come to be eroded from outside.

Case 2

A 21-year-old female patient had suffered a thrombosis of the right internal carotid artery after an acute infection of the middle ear and petrous bone, and 2 years later she suddenly developed a left-sided intracranial bruit which after 2 months was followed by pulsating exophthalmos on that side. Arteriography proved the presence of a carotico-cavernous fistula, but there was no aneurysm. She gave a history, however, of having had many spontaneous haemorrhages in previous years in the subcutaneous tissues, the muscles, and around both orbits, and any interference with her arterial walls (such as during carotid arteriography) had produced very troublesome haemorrhage. Her mother had shown exactly the same type of vascular fragility. Their blood coagulation factors were all quite normal, and sections of her arterial wall examined by light and electron microscopy showed no recognizable abnormality. The nature of this fragility was quite obscure but it seemed possible that the excessive demands made upon the one vessel to supply both hemispheres was such that in the presence of this fragility spontaneous rupture occurred.

Case 3

A mildly hypertensive male patient aged 50 suddenly developed the typical signs and symptoms of a left-sided carotico-cavernous fistula. On examination, however, he presented in addition the full clinical picture of marked hypopituitarism, which had previously passed unnoticed, and without visual field defect. Plain *x* rays of the skull showed a ballooned sella turcica, and by contrast radiography the presence both of a pituitary tumour and of a carotico-cavernous fistula was confirmed. The tumour was removed and the fistula occluded (by Mr. Jack Small) at two operations, and it was seen that there had been a lateral projection of the pituitary tumour which had infarcted and presumably eroded the carotid artery wall.

Two other cases in which lateral projections of pituitary tumours have almost encircled the carotid artery have recently been seen and which, if a more advanced stage had been reached, might have been expected to erode the artery wall and result in a fistula.

Conclusion

It has been the aim of this paper to stress the need for viewing the cavernous sinus and its communicating veins not as rigid structures, but as part of the dynamics of the cerebral circulation. When a fistula occurs, some vessels open up, others close down, and new channels may appear, but throughout all this the patients themselves can respond by showing only a limited clinical picture. It is therefore most important in such cases, if their age and physical condition justifies it, that the most meticulous arteriographic studies should be carried out bilaterally, in order that the precise potential for surgical correction of the lesion may be assessed. Another interesting aspect shown in this series, which is well-known, and is illustrated clearly in Case 1, but for which no very adequate explanation has been arrived at, is that either the process of arteriography, or in other cases the trial period of carotid compression usually required before the carotid is interrupted surgically, may result in closure of either the fistula or its associated channels, so that the symptoms settle down without further interference being required.

Summary

Mechanisms are described by which the so-called bilateral, contralateral, and alternating carotico-cavernous fistulae may be produced by a single arteriovenous communication. Attention is also drawn to two unusual pathological processes which may be the cause of such fistulae.

I am most grateful to Dr. Philip Moxon for carrying out the arteriograms on these patients; to Mr. I. S. Chatha for drawing my attention to the contralateral fistulæ; and to Mr. E. Lowe for the diagrams.

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Neutralizing pattern deviations in ocular motility

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Patients are frequently seen who show heterotropias on gaze in opposite directions, such as an esotropia on looking right and an exotropia on looking left, or a right hypertropia on looking up and a left hypertropia on looking down. These antipodal deviations may occur naturally as a congenital derangement, or may develop as a result of surgery or trauma (Urist, 1964). Fortunately, in most cases, they balance one another so that the eyes become straight, that is, vertically and horizontally aligned, in some neutral position of gaze. Because of this balancing tendency and the ability to develop straight eyes, I call them "neutralizing pattern deviations".

More than half of about 4,000 cases of strabismus examined over the past 20 years have had at least one type of neutralizing pattern deviation. To my knowledge there exists no comprehensive report on all types of neutralizing deviations, no classification, and no nomenclature for discussing them. In this paper I shall classify, discuss, and illustrate the types of neutralizing deviations I have seen.

Somewhere between the opposite directions of gaze in which opposite deviations occur is the "neutral position" where binocular vision is achieved. It may be a large area or a point, the neutral point, depending on the patient's amplitude of fusion.

The neutral position is most commonly located in the primary position, in which the eyes and the head are directed straight ahead. In some cases it is located in an eccentric position and results in a dissociation between the position of the eyes and that of the head. In these cases the head is turned, the direction depending on the position of the neutral point when the eyes are directed straight ahead. It may be a head turn to the right or left, a head tilt to the right or left shoulder, a head bend up or down, or any combination of these.

Cogan (1967) described the neutral point in opposite rapid component nystagmus on gaze in opposite directions as follows:

> The typical motor defect type of nystagmus shows a jerky nystagmus on gaze to either side with the fast component in the direction of gaze. At some neutral point between, the eyes are relatively stationary. The neutral point may be where the eyes are directed straight ahead or eccentrically. The vision is usually normal at the neutral point and the patients with this type of nystagmus habitually turn their heads so that the eyes are maintained in a position of relative rest.

Antipodal heterotropias of various degrees may occur in every position of gaze, often at the same time in the same patient. The diversity of these deviations sometimes requires study to determine whether the eyes can be straight in some position. The following classification of these complex neutralizing pattern deviations will enable the oculist to recognize them more readily.

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Classification

I. Neutralizing horizontal deviations on:

A. VERTICAL GAZE

(*1*) *Neutralizing V pattern* — exotropia up, esotropia down, with head bend up or down if the neutral position is eccentric (See Cases 1, 3, and 7).

(*2*) *Neutralizing A pattern*—esotropia up, exotropia down, with head bend up or down if the neutral position is eccentric (See Case 2).

B. LATERAL GAZE—esotropia on looking right, exotropia on looking left, or *vice versa*, with a head turn to the right or left if the neutral position is eccentric (See Cases 3 and 7).

C. DISTANCE AND NEAR—exotropia for distance, esotropia for near, or *vice versa* (See Cases 1, 3, and 7).

II. Neutralizing vertical deviations on:

A. VERTICAL GAZE—left hypertropia on looking up, right hypertropia on looking down, or *vice versa*, with a head tilt, turn, bend, or any combination thereof, if the neutral position is eccentric (See Cases 4 and 6).

B. LATERAL GAZE

(*1*) *Bilateral elevation in adduction*—right hypertropia on looking left, left hypertropia on looking right (See Cases 1 and 7).

(*2*) *Bilateral depression in adduction*—right hypertropia on looking right, left hypertropia on looking left, with a single or combined head deviation if the neutral position is eccentric (See Case 2).

C. OBLIQUE GAZE—elevation and depression of the same eye in adduction on looking in the same direction obliquely up and down (See Cases 4, 5, and 6).

D. HEAD TILT—right hypertropia on tilt to the right, left hypertropia on tilt to the left, or *vice versa*. When the opposite hypertropias are of equal magnitude, the neutral position is usually in primary position. When one hypertropia is greater, the neutral position may be attained by a head tilt to the side of the smaller deviation (See Case 7).

Case reports

Case 1, an 11-year-old girl (Fig. 1) with an intermittent right esotropia since 3 years of age, exhibited the following three neutralizing pattern deviations:
Exotropia for distance, esotropia for near;
Exotropia on looking up, esotropia on looking down;
Right hypertropia on looking left, left hypertropia on looking right.
The neutral position was looking straight ahead.

Case 2, an 11-year-old girl (Fig. 2), who was moderately hypermetropic, with a congenital intermittent accommodative right esotropia, exhibited two neutralizing pattern deviations: a neutralizing A pattern, and bilateral depression in adduction.
Wearing +3·50 D sph. lenses, her neutral position was looking straight ahead where she achieved stereopsis.

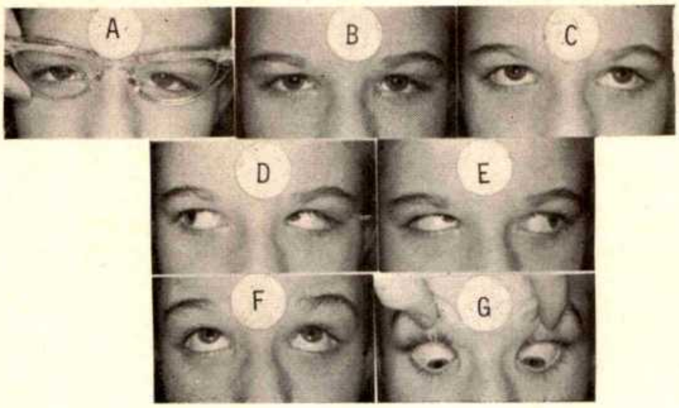

FIG. 1 *Case 1*

(*a*) Eyes straight in primary position with glasses.

(*b*) 5° esotropia for near without glasses.

(*c*) 10° exotropia for distance without glasses.

(*d, e*) Bilateral elevation in adduction.

(*f*) 10° exotropia on looking up.

(*g*) 10° esotropia on looking down.

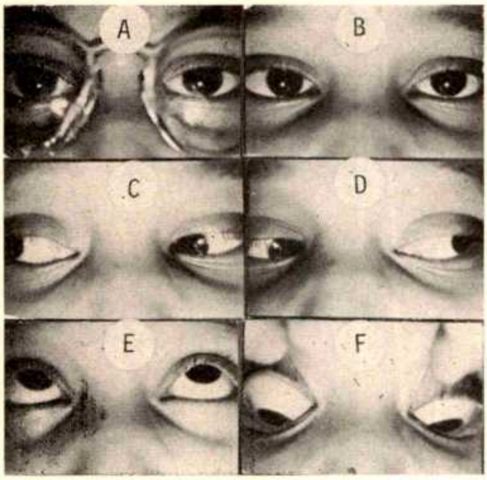

FIG. 2 *Case 2*

(*a*) Eyes straight with glasses in primary position.

(*b*) 15° right esotropia for near without glasses in primary position.

(*c, d*) Bilateral depression in adduction.

(*e*) 15° right esotropia on looking up.

(*f*) 15° right exotropia on looking down.

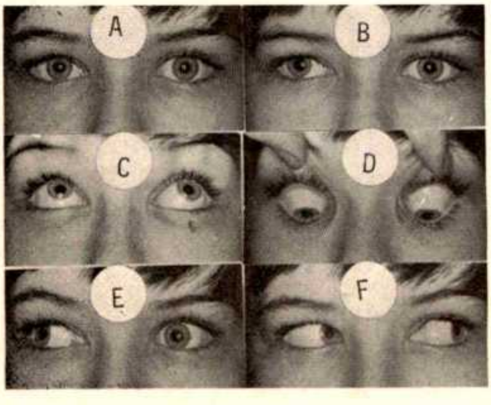

FIG. 3 *Case 3*

(*a*) Slight right esotropia for near.

(*b*) 15° of right exotropia for distance.

(*c*) 15° left exotropia on looking up.

(*d*) Eyes straight on looking down.

(*e*) Exotropia on looking right.

(*f*) Slight esotropia on looking left.

Case 3, a 13-year-old boy (Fig. 3), after surgery for an esotropia which began at age 7, developed a horizontal neutralizing pattern of esotropia on looking right and exotropia on looking left. His neutral position was about 10° left of centre. Consequently he turned his head to the right. When his head was held straight he had an exotropia with crossed diplopia. The following surgical procedures had been carried out: at age 7, a 5 mm. recession of the left medial rectus muscle, and at age 11, a re-recession of the same muscle to 11·5 mm. from the limbus combined with a resection of the left lateral rectus muscle.

A 5 dioptre base-out prism was placed before the right eye and a 5 dioptre base-in prism before the left eye to eliminate the head turn to the right (Fig. 4), and the following three neutralizing pattern deviations were then observed:

Exotropia on looking up, esotropia on looking down;

Esotropia for distance, exotropia for near;

Exotropia on looking right, esotropia on looking left.

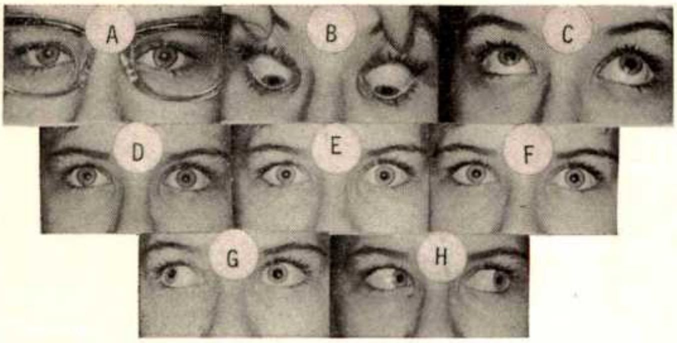

FIG. 4 *Case 3 after application of prisms*

(*a*) Eyes and head straight in primary position when wearing prisms.

(*b*) Esotropia on looking down.

(*c*) Exotropia on looking up.

(*d*) Right exotropia for distance.

(*e*) Eyes straight.

(*f*) Right esotropia for near.

(*g*) Exotropia on looking right with underaction of the left medial rectus muscle.

(*h*) Esotropia on looking left.

Cases 4, 5, and 6 all showed elevation and depression of one eye on looking obliquely up and down (Fig. 5, opposite). Their neutral positions are shown in 5 (*a*), (*f*), and (*j*) respectively.

Case 4 was examined one year after an untreated blowout fracture of the right orbit.

Case 5 showed Duane's retraction syndrome of the left eye.

Case 6 had residual long-standing right IIIrd nerve paralysis.

Case 7, a 10-year-old girl (Fig. 6, opposite) with congenital intermittent esotropia and head tilt to the left, exhibited three types of horizontal and two types of vertical neutralizing pattern deviations:

HORIZONTAL DEVIATIONS Exotropia for distance, esotropia for near; exotropia on looking up, esotropia on looking down; exotropia on looking right, esotropia on looking left.

VERTICAL DEVIATIONS Right hypertropia on looking left, left hypertropia on looking right; right hypertropia on head tilt to the left, left hypertropia on head tilt to the right.

Prism cover measurements with the head tilted to the right:

ET $12^{\triangle}$, LH $10^{\triangle}$; and with the head tilted to the left: ET $12^{\triangle}$, RH $4^{\triangle}$.

With the head tilted a little to the left the patient maintained a neutral position on looking straight ahead.

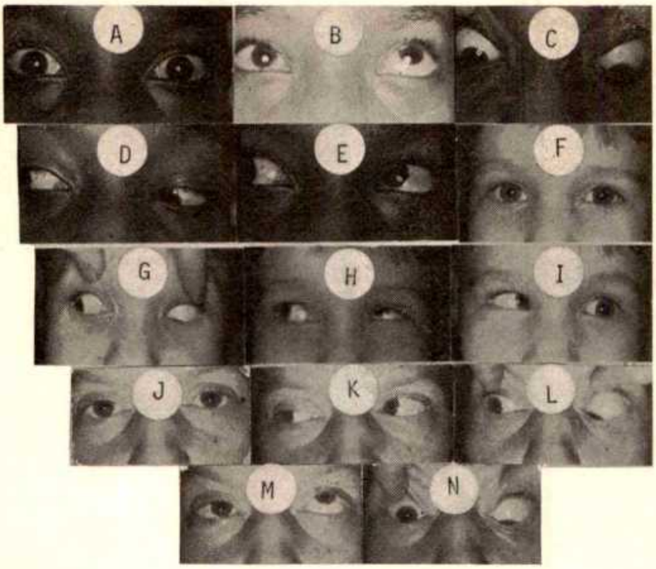

FIG. 5 *Cases 4 to 6*

Case 4

(*a*) Neutral position on looking straight ahead with head slightly tilted to the right shoulder

(*b*) Left hypertropia on looking up with diplopia.

(*c*) Right hypertropia on looking down with diplopia.

(*d*) Depression of left eye in adduction.

(*e*) Elevation of left eye in adduction.

Case 5

(*f*) Neutral position on looking straight ahead with slight head turn to the left.

(*g*) Depression of left eye in adduction.

(*h*) Elevation of left eye in adduction with narrowing of the left palpebral fissure.

(*i*) Limitation of left eye in adduction with widening of the left palpebral fissure.

Case 6

(*j*) Neutral position on looking straight ahead.

(*k*) Elevation of left eye in adduction.

(*l*) Depression of left eye in adduction.

(*m*) Left hypertropia on looking up.

(*n*) Right hypertropia on looking down.

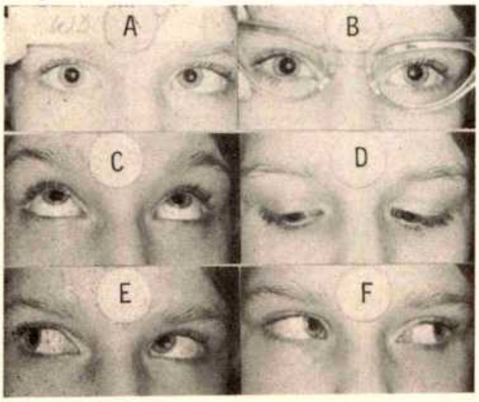

FIG. 6 *Case 7*

(*a*) 10° left esotropia and 5° left hypertropia for near.

(*b*) 5° left exotropia for distance with glasses.

(*c*) 5° exotropia on looking up.

(*d*) 10° left esotropia on looking down.

(*e, f*) Bilateral elevation in adduction, greater in the left eye; exotropia on looking right, slight esotropia on looking left.

Comment

In many cases the eyes may be only intermittently straight in the neutral position. At the time of examination they are often dissociated. Then the various combinations of opposite kinds of vertical and horizontal tropia deviations can become very confusing. Keeping in mind the above classification and looking for some position where there may be a neutral point and where the patient may have fusion helps to clarify the diagnosis.

Fusion was elicited in six of the seven patients described above. It is the most important factor in the presence of heterotropias for developing and maintaining a neutral position with or without turning the head.

Where large heterotropias occur it is interesting to consider how alignment of the eyes is adjusted so that fusion can become operative to develop a neutral position. One common way is by trial and error. Patients with diplopia, or what some call a visual blur, adopt various positions of gaze to try to clear their vision. Once they find a neutral position they tend to maintain it or to assume it when desiring to see clearly or binocularly.

Another method is to use what appears to be an eye-centering reflex movement which comes into play when the lids are tightly shut. Patients with both horizontal and vertical deviations had volunteered that they could straighten their eyes and eliminate their diplopia or blur by blinking, and this observation was confirmed on examination. Consequently I began the practice, in examining patients with derangements of ocular motility, of testing the effect of closing the eyes. I found that large deviations, both vertical and horizontal, could be made to disappear by this manoeuvre. Careful observation of deviating eyes after thev had been kept tightly shut revealed that in most cases they would appear momentarily straight before returning to the original deviation; in other cases they would remain straight until dissociated.

Bender and Shanzer (1964) considered that centering movements of the eyes in monkeys were a distinct form of eye movement. They found that, upon electric stimulation of certain areas of monkeys' brains, regardless of the position of the eyes before stimulation, each eye would move toward the centre of the orbit.

One may speculate that these centering movements are also important in human physiology, and it is certain that they require further study.

Summary

Neutralizing pattern deviations are antipodal deviations (such as exotropia on looking left and esotropia on looking right, or left hypertropia on looking up and right hypertropia on looking down) which can balance each other so that the eyes become vertically and horizontally aligned in some neutral position. The neutral position can be a point or a large area depending on the amplitude of fusion. It is most often found in the primary position, and when it is in some eccentric position of gaze it is usually accompanied by a turn or tilt of the head.

Neutralizing pattern deviations may be classified as horizontal or vertical and by the direction of gaze, vertical, horizontal, oblique, or torsional, in which they occur.

Two methods by which patients with antipodal deviations achieved ocular alignments are described.

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Cataracts of dysplasia epiphysialis punctata

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This rare disease of cartilage in infants has been recorded under various names since it was first described by Langhans (1893). Amongst these are chondrodystrophia calcificans congenita, chondrodystrophia punctata, stippled epiphyses, foetal epiphyseal calcinosis, chondrodystrophia calcarea, chondroangiopathia calcarea seu punctata, and chondrodystrophia hypoplastica calcinosa.

Conradi (1914) described the radiological appearance of the condition. He thought it was an atypical form of achondroplasia, and it was not until much later that Fairbank (1927) distinguished the two conditions.

In 43 cases described by Yakovac (1954), 25 per cent. had bilateral cataracts; these were present in Conradi's original case. Optic atrophy has also been described in this condition.

The disease, as the name suggests, has a striking radiographic appearance, the irregular calcification of the cartilage of the epiphyses giving a characteristic stippled appearance. This stippling may be generalized throughout the cartilage or limited to an area around the centre of ossification. It has been reported to disappear later in childhood (Paul, 1954).

In association with this abnormality there are usually other defects. The infants are frequently dwarfs of the short limb type. There may be contractures of the limbs, talipes, kyphoscoliosis, "saddle-shaped" nose, enlargement of the skull, and mental deficiency, and the skin may be thickened. In general the infant is weak and usually fails to thrive, so that death from intercurrent infection in the first 12 months of life is almost the rule.

Case report

A baby boy 11 weeks old was referred for investigation because of loss of weight and a history of not sucking well. He weighed 7 lb. (3·4 kg.) and was 19½ in. (50 cm.) in length. The head appeared large in proportion to the body length with marked parietal and occipital eminences. The head was 14 in. (35·5 cm.) in circumference and in general the baby appeared stunted. Examination of the eyes showed bilateral mature cataracts.

There were marked contractures of the limbs and limitation of movement of the shoulders, elbows, hips, and knees. The legs were kept in marked adduction. There was a rash on the skin of the chin, cheeks, and neck. The liver was enlarged. The facies were abnormal, rather suggesting a mongoloid condition. Mentally the baby was apathetic and a generalized weakness was obvious. X-ray examination of the skeleton showed stippling of the epiphyses of the long bones, and the femoral and humeral shafts were short and thick.

Pathology The baby died soon afterwards and an eye was obtained for histological examination. It measured 16 × 17 mm. Microscopic examination showed the cornea to be normal except that Descemet's membrane was rather thinner than usual. The iris was normal but the ciliary processes were very poorly developed.

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The main pathology was seen in the lens (Figure). The trouble lay mainly in the equatorial and subcapsular regions. The equatorial lens epithelium was abnormal in that it consisted of large swollen cells proliferating but not forming any true lens fibres. The more superficial of these cells showed large vacuoles filled with clear fluid displacing the nuclei towards the centre of the lens. The anterior polar region gave a picture of normal subcapsular epithelial cells, but the abnormal lens fibres arising from the equator extended in a haphazard fashion deep in this epithelium right up to the anterior pole. These abnormal fibres also extended for a considerable distance in the posterior portion of the lens.

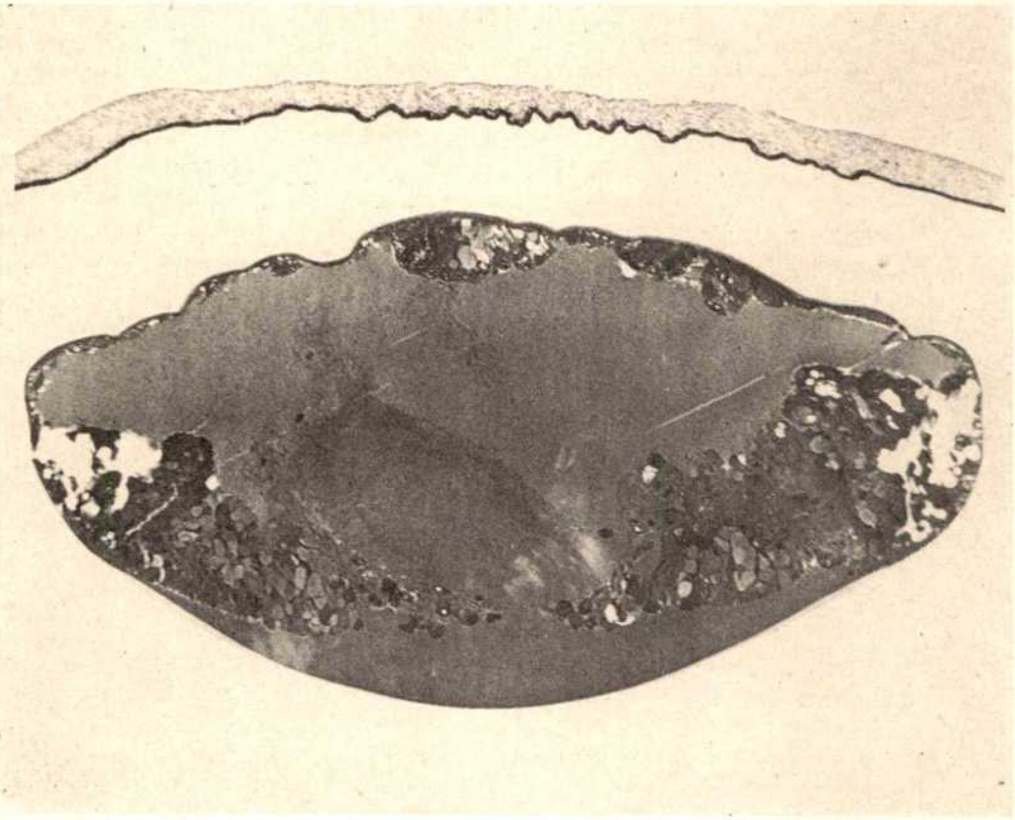

FIGURE *Site of cataract and vacuolated abnormal lens fibres*

The centre of the lens became more normal as it was followed inwards, except for one area where an unidentifiable abnormal material was deposited between the fibres. No crystals were to be seen in the lens substance. The lens capsule was well developed and normal. The retina showed some oedema of the nerve fibre layer and a small subretinal haemorrhage. The optic nerve was normal. The extraocular muscles were infiltrated by small round cells and some endothelioid cells.

Discussion

Histological examination of the lens showed that the condition was a primary malformation of the secondary lens fibres and not a degeneration of the originally normal lens fibres. From the position of the abnormalities in the lens in relation to other lens structures, it appeared that the noxious agent began to act in about the fifth or sixth month of foetal life, and that it had continued to act after birth until death supervened.

In considering the nature of the noxious agent there are several points to be discussed. The vacuolation and swelling of the cells and fibres of the lens epithelium suggest that the agent acts on the metabolism of the cell. The disease begins in about the fifth month of intrauterine life, at which time a changeover in the mechanism of the nutrition of the lens is occurring. Up to this time the nutrition of the lens is effected by the tunica vasculosa lentis but later, after this has atrophied, the lens is dependent on the aqueous humour for its metabolic needs. It would appear that the former mode of nutrition is adequate for the growing lens, but that trouble begins when the lens fibres are required to obtain their nourishment from the aqueous.

Lenticular metabolism when mediated by the aqueous humour is effected by a complex system of enzymes. The energy requirements of the lens are served mainly by carbohydrate metabolism, in particular glucose metabolism, by a very complicated series of reactions, each apparently with its own enzyme to act as a catalyst. It has been shown experimentally that young animals are more susceptible than adults to nutritional cataract formation. It appears likely that the cataracts in dysplasia epiphysialis punctata are produced by an enzyme deficiency which may be congenital. The poor development of the ciliary processes in the case described above may support this latter theory.

Any hypothesis advanced to explain the formation of these cataracts must also explain the other lesions of the syndrome which are largely lesions of cartilage.

Hyaline cartilage has a high mucopolysaccharide content (chondroitin sulphate) and it is without a blood supply; like the lens it has to obtain its nutritional requirements from the surrounding body fluids. Its metabolic processes are therefore somewhat similar to those of the lens and it is probable that in dysplasia epiphysialis punctata both the formation of abnormal lens fibres causing cataracts and the abnormality of the epiphyseal cartilage are due to a common nutritional disorder such as an enzyme deficiency.

Summary

A case is reported of dysplasia epiphysialis punctata with cataract formation. The histological structure of the cataract is described and a possible aetiology of the condition is discussed.

The author wishes to thank Prof. Ida Mann and Mrs. Antoinette Pirie for their generous help with this paper, and also Dr. K. Campbell for the clinical notes and specimen.

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U-shaped retinal tear

Associated with a presumed malignant melanoma of the choroid

M. A. BEDFORD AND A. H. CHIGNELL

Moorfields Eye Hospital, London, E.C.1

The purpose of this paper is to report a case of presumed malignant melanoma of the choroid associated with an overlying U-shaped tear. This type of retinal hole is commonly found in association with a simple retinal detachment and is thought to be caused by vitreous traction on the retina at the point of the tear. This kind of tear has not been reported previously in connexion with a malignant melanoma of the choroid, although other types of retinal holes have been described in association with a malignant melanoma. This is the first case of any retinal hole photographed *in vivo* in the presence of a malignant melanoma. Lister (1924) was able to state that the presence of a retinal hole in an eye with a retinal detachment precluded the presence of a malignant melanoma. This was supported by Duke-Elder (1940), but later Duke-Elder (1967) stated that a few cases of malignant melanoma with a hole in the same eye had been reported. Berson, Bigger, and Smith (1967) reviewed the literature and found thirteen cases and added another of his own; in no single instance was a U-shaped (traction) tear reported.

Case report

A 56-year-old woman was first seen at another hospital with a history of floaters in the right eye. These symptoms had been present for several months. Examination revealed a solid upper temporal detachment with "retinal holes". The lesion was round, grey, and speckled with pigment. She was seen by a number of senior ophthalmologists who agreed upon the diagnosis of a malignant melanoma. She was treated by a ring of light coagulation to try and limit the extension of the detachment and then referred to London.

Examination

A month later she was found to have a U-shaped retinal tear overlying a solid detachment of the retina in the upper temporal region of the right eye (Figure). The solid appearance of the underlying tumour was considered to be typical of a malignant melanoma by several observers. The left eye was normal. Diagnosis was greatly facilitated by examination with the indirect ophthalmoscope.

Therapy

The tumour was treated by the application of a radioactive cobalt plaque (Stallard, 1966) and the retinal detachment, which persisted after satisfactory tumour resolution, was treated at a later date by a Lincoff procedure (Lincoff, Baras, and McLean, 1965); fluid was not released.

Result

18 months later the retina was flat.

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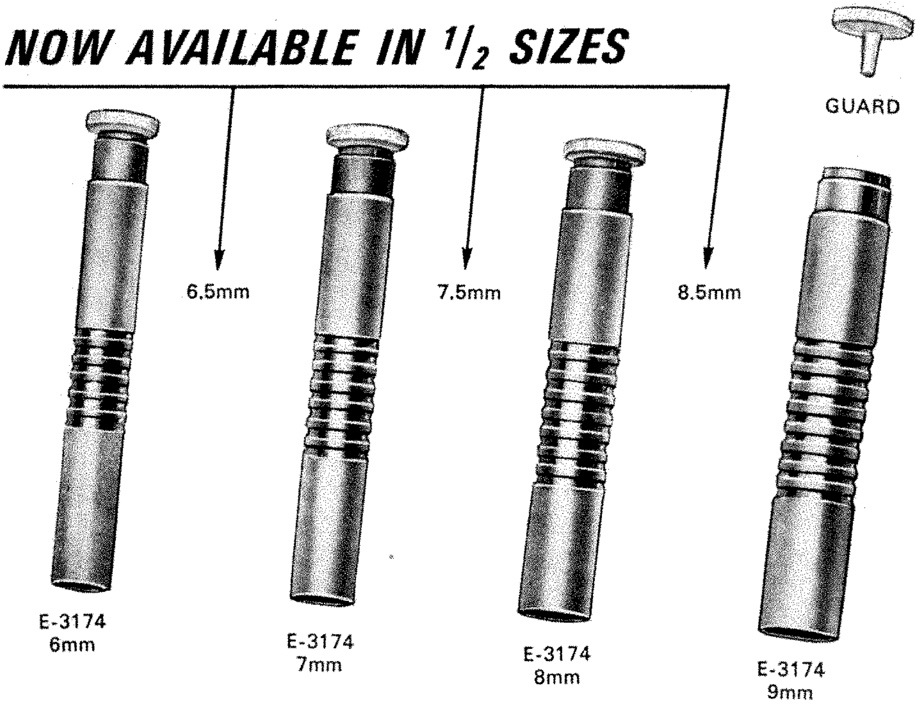

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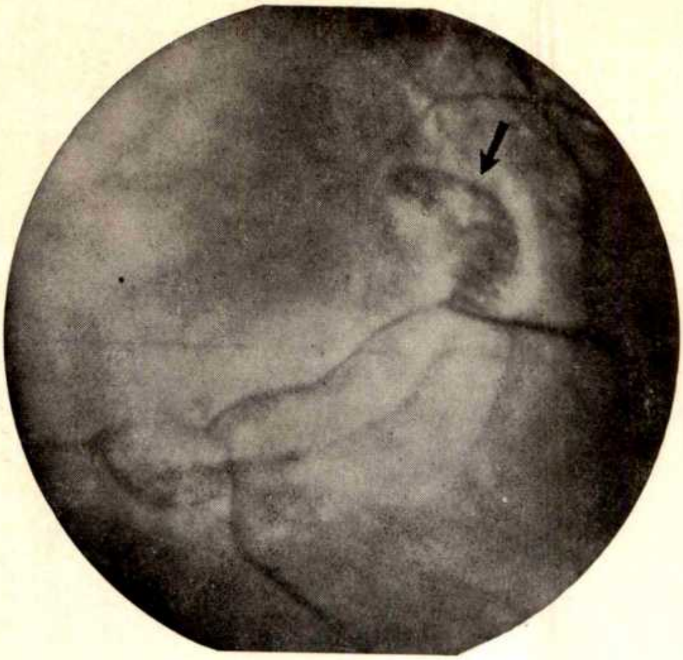

FIGURE *Arrow points to edge of clinical U-shaped tear through which was seen the typical surface of a malignant melanoma*

Discussion

Berson and others (1967) reported a round hole in an area of serous detachment associated with but not over a malignant melanoma.

Bierman (1958) reported a case of giant retinal tears in an eye with a malignant melanoma, but its relationship to the tumour was not clear.

Boniuk and Zimmerman (1962) and McGraw (1951) noted retinal holes in eyes with malignant melanomata, but the holes were not related to the tumours anatomically.

Manschot (1964) described a "straight retinal rupture" associated with a malignant melanoma. Manschot (1965) also described the histology of a retinal hole, not seen clinically, but found on pathological examination. This hole lay in a degenerate retinal cyst overlying the tumour.

Morgan (1956) reported a case of malignant melanoma with a retinal hole situated elsewhere in the retina. The tumour in his case was treated by enucleation and some time later the other eye suffered a simple detachment.

Conclusion

A unique case of a U-shaped retinal tear directly overlying a presumed malignant melanoma is described. This indicated that this type of retinal hole, which is normally associated with vitreous traction and simple retinal detachment, does not necessarily exclude the possibility of an underlying malignant melanoma. The binocular indirect ophthalmoscope proved to be invaluable as a diagnostic instrument.

We wish to thank Miss Wendy Taylor for secretarial assistance, and the Audio-Visual Department of the Institute of Ophthalmology for providing the illustration.

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Orbital rhabdomyosarcoma in an infant

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Rhabdomyosarcoma is a rare primary neoplasm in childhood which usually occurs at the age of 7 to 8 years (Jones, Rees, and Kraut, 1966). The youngest patient so far recorded was 2 years old (Lederman, 1956).

Case report

A 1-year-old male Hindu infant was brought to the Eye Out-patient department of Irwin Hospital, New Delhi, on December 14, 1968, with a history of a swelling in the left orbit and protrusion of the eyeball for one month. According to his mother the swelling had first appeared in the lower nasal quadrant of the left orbit and rapidly progressed to the upper nasal quadrant and displaced the eyeball. No history of trauma or any intercurrent infection was available.

Examination There was an eccentric proptosis of the left eye which was displaced forwards, upwards, and outwards (Fig. 1). A soft ill-defined swelling measuring 2 × 1·5 cm. was palpable on the inner aspect of the eyeball along the medial margin of the orbit. The overlying skin was free but the swelling was attached to deeper structures. The movements of the eye were markedly restricted. Cornea, anterior chamber, iris, and pupillary reactions were normal.

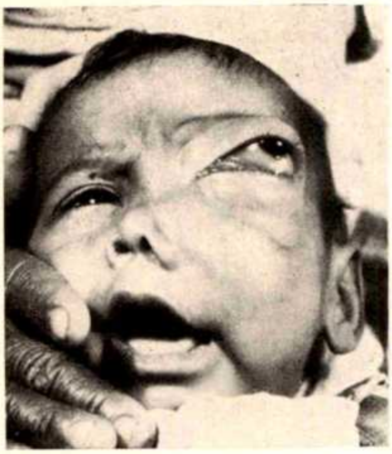

FIG. 1 *Appearance at first examination, showing proptosis*

Fundus examination showed blurring of the disc margins, hyperaemia of optic disc, and increased tortuosity of the retinal vessels in the left eye. Ear, nose and throat examination revealed that the left side of the nose was displaced inwards.

Laboratory investigations Hb 8 g. per cent., leucocyte count 3,100/cu. mm. (polymorphonuclears 64 per cent., lymphocytes 30 per cent., eosinophils 6 per cent.).

X-ray examination of the left orbit showed soft tissue shadow but no bony destruction. The optic foramina were of normal size.

Treatment Tetracycline 125 mg./6 hrly was given by mouth. During the next few days the swelling and proptosis progressed rapidly and the cornea became hazy. Tarsorrhaphy was done, but the stitches gave way and the cornea became ulcerated and perforated. The orbit was explored on

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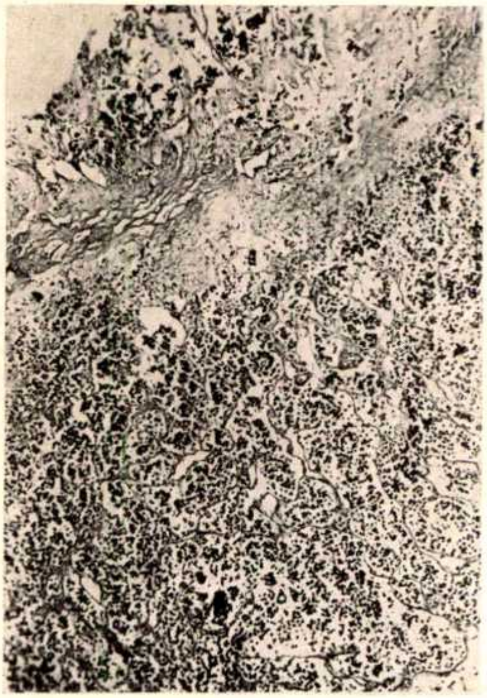
December 18 through a curved incision over the swelling. A soft ill-defined mass was found to extend along the medial wall of the orbit. Part of the tumour was removed and sent for histopathological examination.

Histology The tumour consisted of groups of round to polyhedral cells arranged in an alveolar pattern (Fig. 2). The malignant cells varied in size and had generally a scanty acidophilic cytoplasm which tended to merge with the septa (Fig. 3) and a relatively large hyperchromatic nucleus.

(2)



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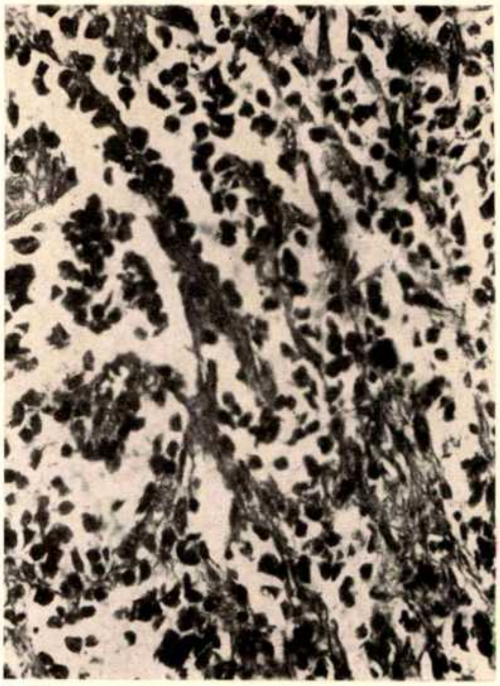


FIG. 2 *Section showing alveolar pattern of tumour. Reticulin.* × 100

FIG. 3 *Section showing thin septa with the tumour cells closely applied to them. The cytoplasm of tumour cells at many places merges with the septa. Haematoxylin and eosin.* × 450

A few multinuclear giant cells were discernible (Fig. 4) and a few mitotic figures were present. The tumour had invaded the vascular channels (Fig. 5). No definite cross-striations could be demonstrated. The histological picture was characteristic of the alveolar type of rhabdomyosarcoma.

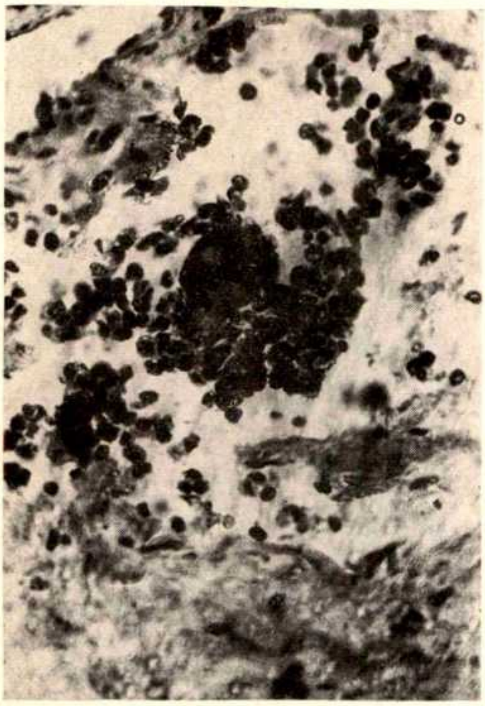
Progress Radiotherapy with cobalt 60 (200 r for 3 min. 11 sec. daily 5 days a week for 8 weeks). The swelling regressed considerably (Fig. 6). Exenteration was contemplated but the parents refused and took the child away against medical advice. They returned, however, after 5 months and examination revealed no further change in the clinical appearance.

Comment

This patient is the youngest so far recorded. The tumour more often involves the right orbit and the most common site is the upper nasal quadrant. In our case the tumour arose from the lower nasal quadrant of the left orbit.

These tumours are considered to be radioresistant (Reese, 1951; Duke-Elder, 1952); Lederman (1956) found them highly radiosensitive though rarely radiocurable. In this case radiation given as primary therapy was followed by regression of the tumour (Fig. 6).

(4)



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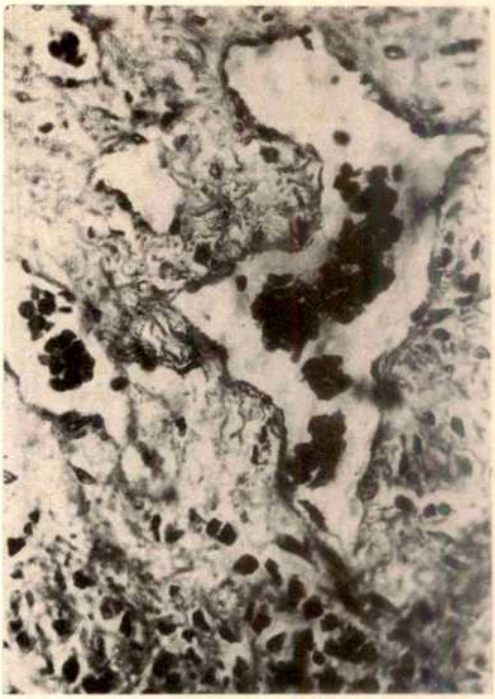

FIG. 4 *Another field of section in Fig. 3 shows a multinucleated giant cell surrounded by several cells showing pleomorphism. Cross-striations could not be demonstrated. Phosphotungstic acid and haematoxylin.* × 450

FIG. 5 *Section showing invasion of a vascular channel. Phosphotungstic acid and haematoxylin.* × 450

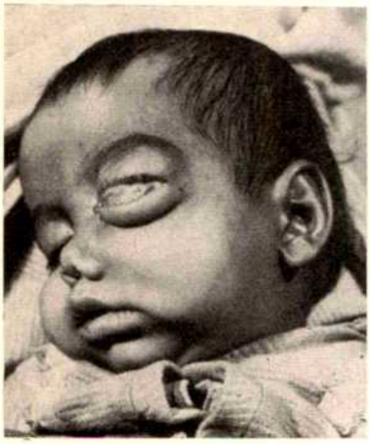

FIG. 6 *Appearance after radiotherapy*

Summary

A case of rhabdomyosarcoma in a 1-year-old child responded to radiotherapy.

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Brit. J. Ophthal. (1970) **54**, 206

Orbital neurilemmoma

Presenting as retrobulbar neuritis

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Neurilemmoma of the orbit is a localized, encapsulated, benign nerve sheath tumour which grows very slowly and possibly intermittently, and has no distinctive clinical features (Reese, 1963). When large enough it causes exophthalmos and sometimes blurring of vision through pressure on the optic nerve (Reese, 1963; Sharma and Kulshrestha, 1961). The motility of the eyeball may also be impaired. This tumour has rarely been recorded in the literature and we have been unable to find any previous report that it may first present with the clinical features of retrobulbar neuritis.

Case report

A Hindu schoolgirl aged 14 years came to the eye out-patient department complaining of defective vision in the right eye for 10 days. The onset had been fairly sudden and was at first painless.

Examination

The left eye and its adnexa were normal, with visual acuity 6/6.

In the right eye the visual acuity was 6/24. There was mild local pain on moving the eye but no limitation of movement. The pain was increased by pressure on the globe. The pupil reacted to light but the contraction was not maintained under bright illumination. The fundus was examined by direct and indirect ophthalmoscopy and appeared to be normal.

Investigation of the visual fields showed a central scotoma which was relative for colours. Skiagrams of the paranasal sinuses and orbits gave no diagnostic information.

The case was thought to be one of retrobulbar neuritis, but a thorough systemic and neurological examination did not reveal any specific cause of the neuritis.

Therapy

The patient was given non-specific treatment with heavy doses of vitamin B_1 and B_{12} intramuscularly and glucocorticoids orally.

Progress

As there was no recovery of vision even at the end of 3 weeks she stopped attending the hospital, but after 3 years she returned complaining of loss of sight in the right eye with exophthalmos which had been gradually increasing for the past 2½ years. She stated that her sight had been steadily diminishing since she had first attended the hospital.

Examination

There was no perception of light in the affected eye. The globe was displaced forwards, upwards, and outwards. Movements were restricted in all directions, especially downwards. The conjunctiva, cornea, and iris were normal. The pupil was dilated and fixed. The optic disc showed pressure type atrophy. Palpation of the orbital margins showed no abnormality, and no orbital mass could be felt even on deep palpation. Skiagrams of the skull, orbits, optic foramina, and paranasal sinuses, and also blood studies were negative.

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Operation

Kronlein's lateral orbitotomy was performed under general anaesthesia and exploration of the orbit revealed a well-encapsulated firm elastic mass located in the lower medial quadrant. Though there was some difficulty because of the situation of the tumour the whole mass could be shelled out with the index finger.

Result

The post-operative period was uneventful, and histopathological examination identified the tumour as neurilemmoma with Antoni cells type-A and type-B (Figure).

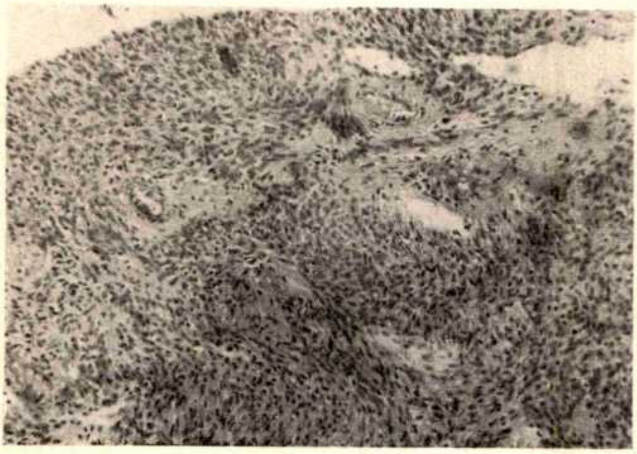

FIGURE *Photomicrograph of tumour tissue, showing fascicular arrangement of cells. Haematoxylin and eosin.* × 100

Comment

It is to be noted that neurilemmomata and other orbital neoplasms may sometimes present as cases of retrobulbar neuritis with no evidence of the presence of a tumour, yet to miss the true diagnosis at this early stage could be disastrous. It is, therefore, imperative to exclude the presence of orbital neoplasm in all cases of retrobulbar neuritis of obscure aetiology. Docter and Kennedy (1948) stated that such tumours were always palpable through the lid and Sharma and Kulshrestha (1961) also palpated a mass through the lid in their cases, but this did not prove to be possible in the present case. Some of the reported cases showed signs indicative of von Recklinghausen's disease, such as pigmented spots over the body, cutaneous nodules, and a dehiscence in the roof of the orbit, but none was present in this case.

Summary

A case of neurilemmoma of the orbit presented as retrobulbar neuritis.

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Brit. J. Ophthal. (1970) **54**, 208

Horizontal sector hemianopia of non-traumatic origin

R. J. S. SMITH

Glasgow

Spalding (1952) described four instances of homonymous hemianopia in which narrow sector-shaped defects occurred in the horizontal meridian, involving part of both upper and lower quadrants, and reaching to the fixation point.

These emerged from a series of 958 penetrating head injuries, mainly gunshot wounds, of which 188 had field defects attributable to injury of the optic radiations or striate cortex, and in which Spalding had precisely localized the path of the missile and the area of visual pathway affected.

He clearly demonstrated that the unusual field picture resulted from damage to the whole horizontal thickness of the intermediate part, *i.e.* that lying midway between the upper and lower margins, of the optic radiation in its anterior part (Fig. 1 E—interrupted line).

The area in question is traversed by a line drawn head to tail through the trigone of the lateral ventricle, at which point the optic radiation forms a relatively flat plate on the lateral aspect of the trigone (Fig. 1 F).

If considered in relation to the skull, the area is posterior to that part of the temporal lobe whereof lesions produce upper partial quadrantopia as described by Meyer (1907) and Cushing (1922), but considered functionally, as part of the visual pathway, it pre-places the Meyer's loop territory. It is in both respects well in front of the posterior optic radiations (Fig. 1 I) where lesions can produce the familiar upper or lower quadrantopias as described clinically by Holmes (1918) and anatomically by Polyak (1934).

The arrangement of fibres in this area is similar to that in the adjacent external geniculate body, where the fibres subserving central vision lie above, those for peripheral vision below, and those for intermediate vision between the two.

The left visual half field is shown in Fig. 1 A, with central vision indicated by a stippled pattern, peripheral vision by black, and intermediate vision by white. The associated fibres in the right external geniculate body are similarly indicated (Fig. 1 B).

If the external geniculate body is visualized as being turned clockwise through 90° (Fig. 1 C), and is thought of as consisting of malleable material which is then compressed from side to side between the finger and thumb (Fig. 1 D), it becomes easier to understand the position. The conception of continued lateral compression (Fig. 1 G) may be used to provide a mental picture of conditions existing in the posterior radiations (Fig. 1 H), where the radiation is a horseshoe-shaped structure embracing the posterior horn of the ventricle.

It is not difficult to see how a lesion involving the whole horizontal thickness of the anterior radiation (Fig. 1 E) will produce field defects as found in Spalding's four patients and in the patient described below.

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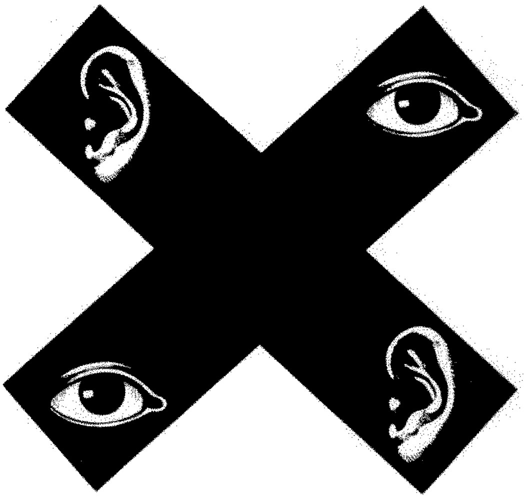

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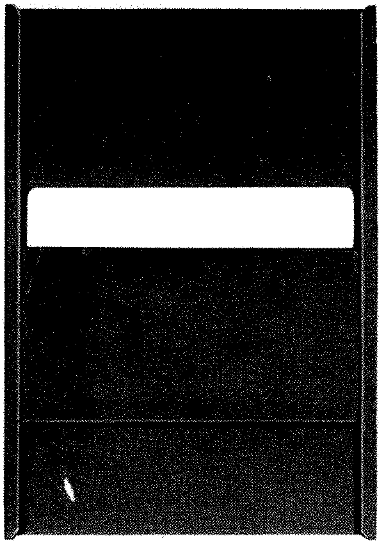

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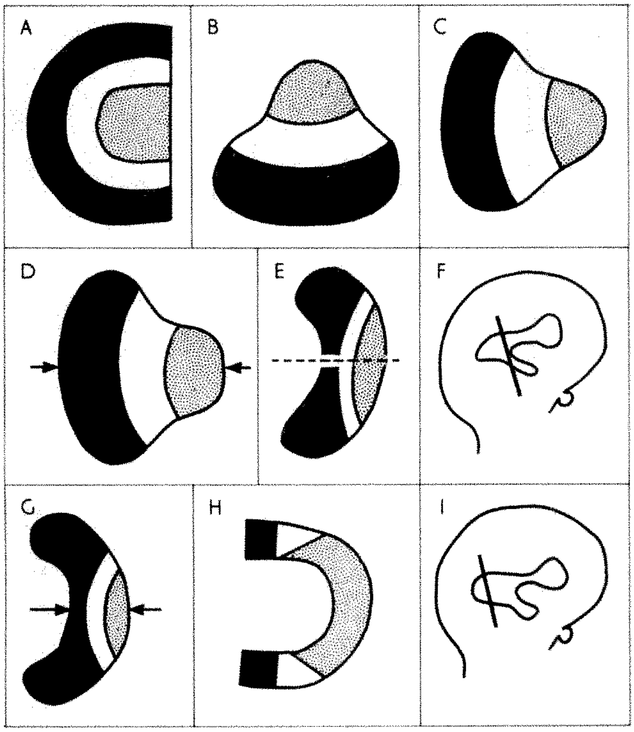

FIG. 1 *Drawings intended to provide a simple reminder of the relevant anatomy in horizontal sector hemianopia*

The subject is discussed by Scott (1957) with direct reference to Spalding's original diagrams. These illustrate in detail the distribution of the relevant visual fibres.

Case report

A hotel manager, born in 1921, became aware in March, 1959, of a sudden tingling sensation in the back of his head and neck, a roaring sound in the ears, and a peculiar taste in his mouth 'like an anaesthetic". He then lost consciousness and fell to the ground. There was no incontinence. He was unconscious for several hours. Complete recovery resulted. Simple investigations were negative.

In March, 1960, similar premonitory symptoms were experienced but passed off rapidly. There were no abnormal neurological signs. Electrocardiography, electroencephalography, and air encephalography gave negative results. Temporal lobe epilepsy was diagnosed.

In April, 1963, the patient complained of sudden severe right-sided temporal headache and blurring of central vision. He quickly recovered and did not lose consciousness. The only neurological sign was some inco-ordination of the left arm. Bilateral carotid and vertebral angiograms were normal. Fundi and discs were normal. Central visual acuity was intact in each eye on 2 May, 1963. The central visual fields to 6/1000 white, 6/1000 red, and 2/1000 red targets were as recorded (Fig. 2).

The illness was attributed to a vascular accident involving the anterior optic radiation on the right side.

The patient returned to work some months later, and has not sought further advice. When traced on 28 January, 1969, he explained that he still has occasional "queer turns" in which he "feels faint with a taste in the mouth like chloroform", but these had not interrupted his work. He drives a car and then only is he slightly aware of his visual defect. Eye examination showed normal visual acuity, and with targets equivalent to those of 1963 visual field defects as recorded (Fig. 3).

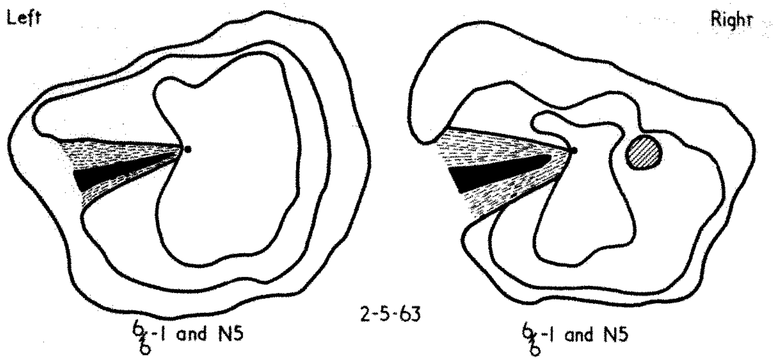

FIG. 2 *Central visual fields one week after presumed cerebro-vascular accident.*

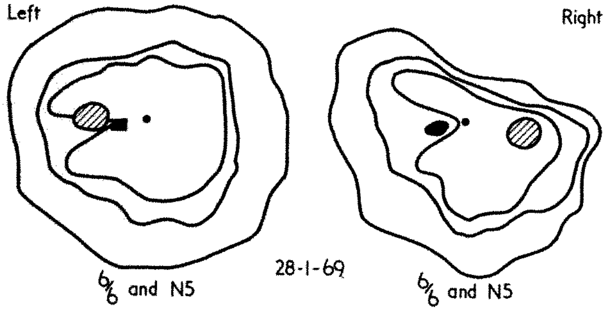

FIG. 3 *Central visual fields 6 years after presumed cerebro-vascular accident*

Summary

A case is described of non-traumatic hemianopia showing the picture elicited by Spalding (1952) in four patients who had sustained gunshot wounds involving the whole horizontal thickness of the intermediate part of the optic radiation in its anterior part.

The lesion in the present patient has been attributed to a vascular accident. Review after 6 years shows an improvement in the visual fields with a decrease in density of the triangular sector defects and residual hemianopic scotomata at their apices.

The patient leads a normal life but suffers from mild temporal lobe seizures.

I am indebted to the surgeons of the Institute of Neurological Sciences, Glasgow, through whom the opportunity came to make these observations.

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Brit. J. Ophthal. (1970) **54**, 211

Rat bite orbital cellulitis

R. DIWAN, D. K. SEN, AND G. C. SOOD
Department of Ophthalmology, Maulana Azad Medical College, New Delhi, India

Apart from transmitting various specific diseases (Manson-Bahr, 1960), rat bite is known to cause an inflammatory local reaction which may rarely go on to the stage of cellulitis. A case is reported below in which the bite of a house-rat near the inner end of the left eyebrow caused orbital cellulitis and proptosis.

Case report

A Hindu female aged 25 years was seen at the Eye Out-Patient Department of Irwin Hospital, New Delhi, on February 2, 1969, with the complaint of pain and protrusion of the left eye following a rat bite over the left eyebrow about one week earlier. This was associated with fever and other constitutional disturbances. The body temperature was 102°F., blood pressure 120/80, pulse rate 120/min. The left preauricular node was palpable and tender.

Examination There was a small indurated swelling on the inner end of the eyebrow which was quite tender to the touch. The left eye was proptosed. Both lids were oedematous with moderate conjunctival chemosis. Ocular movements were markedly restricted in all directions. The visual acuity in the left eye was counting fingers at 1 m. with accurate projection of light. Fundus examination showed slight hyperaemia of the disc with dilation and tortuosity of the veins. Exophthalmometry (Hertel's method) showed the right eye 14 mm. and the left eye 27 mm.

Laboratory Investigations Hb 8 g. per cent. Total leucocyte count 11,000 per cu. mm. (polymorphonuclears 48 per cent., lymphocytes 51 per cent., eosinophils 1 per cent.). Erythrocyte sedimentation rate 93 mm./1st hour (Westergren).

Blood cultures, serological tests for syphilis, and urine examination were negative. Skiagrams of the paranasal sinuses, orbits, and optic foramina showed no abnormality.

Treatment The patient responded well to intravenous achromycin 250 mg. 6 hrly. The temperature returned to normal within 2 days, and the proptosis began to regress and disappeared completely in 7 days.

Result The patient was then discharged and has remained symptom-free.

Comment

Rat bite is not uncommon in Indian villages but the victims rarely need hospital care, and the eyebrow is a very uncommon site. It is rare for the organisms in the buccal cavity of a house rat to be so virulent as to cause such severe cellulitis.

Summary

Orbital cellulitis caused by a rat bite at the inner end of the left eyebrow responded very well to intravenous injections of a broad-spectrum antibiotic.

Reference

MANSON-BAHR, P. H. (1960) "Manson's Tropical Diseases", 15th ed. Cassell, London

Received for publication August 7, 1969
Address for reprints: Department of Ophthalmology, Maulana Azad Medical College, New Delhi, India

Brit. J. Ophthal. (1970) **54**, 212

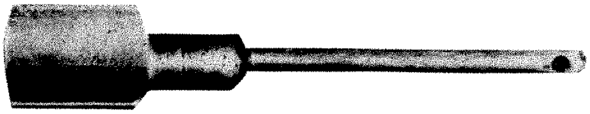
Modified lens aspiration needle

C. T. HART
University of Sheffield

The use of a needle for aspiration of soft lens material is now an accepted surgical procedure. Previous descriptions of this operation have generally required a specially constructed needle. A simple modification to a standard needle which can be easily performed in an engineering workshop is described below.

Construction

The shaft of a standard anaesthetic mixing needle has been reduced to a length of 20 mm. The end of the needle has been closed with silver solder and rounded off with a smooth polished finish; a side opening has been introduced close to the end of the needle with a diameter of 1·1 mm.



Operative technique

A cruciate incision of the anterior lens capsule is made with a Barkan goniotomy knife, the pupil having been fully dilated. This incision is enlarged with a keratome or a broad needle and the large-bore aspiration needle is introduced into the anterior chamber attached to a 5 ml. syringe of normal saline. Aspiration and irrigation are then performed through the same needle alternately. Clearing of the pupillary area of soft lens matter can easily be seen ophthalmoscopically. Two silk sutures are inserted at the limbal incision and the anterior chamber is reformed with saline. The administration of topical mydriatics and steroids can then be started immediately.

The advantages of a side-bore aspiration needle discussed by Gass (1969) have been verified by the present author. The large bore of the present needle permits rapid aspiration of lens material with less effort or suction and therefore shortens operative time and possible trauma. The side opening allows greater manœverability within the anterior chamber with less risk of damage to the posterior capsule and vitreous face than does direct end-on aspiration. This needle has now been in use by the author and other surgeons for over a year.

Summary

A modified side-bore cataract aspiration needle has been evolved from a standard anaesthetic mixing needle.

My thanks are due to Mr. A. Stanworth for his help and advice in the preparation of this paper, and to the Medical Workshop, University of Sheffield.

Reference

GASS, J. D. M. (1969) *Arch. Ophthal.* (*Chicago*), **82**, 87

Received for publication October 20, 1969
Address for reprints: Department of Ophthalmology, Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF

Brit. J. Ophthal. (1970) **54**, 213

Book reviews

Glaucoma. By RAYMOND ÉTIENNE. 1969. Pp. 630, 176 figs. Diffusion Générale de Librairie, Marseille.

In 1961 Étienne in collaboration with Albert Ourgaud presented the annual "Rapport" of the French Society of Ophthalmology on the "Functional Investigation of the Glaucomatous Eye"—the subject chosen for that particular year. Étienne's new book on glaucoma is an extension of his work on that monumental thesis, and is a beautifully produced volume worthy of the high esteem in which the members of the Lyons School are held.

Apart from the striking colour illustrations (which have been printed with a plasticized glossy finish to enhance their contrast), the book is a mine of thought-provoking information, and will repay any effort involved in reading the French. It is written in concise style and is divided into thirteen sections covering all aspects of glaucoma. The latest views on the anatomy and physiology of glaucoma are dealt with in detail, as are methods of clinical investigation, such as tonometry, tonography, the perilimbal suction cup, gonioscopy, and static and dynamic perimetry. The chapter on the classification of glaucoma includes a lengthy list of the common forms and rare syndromes associated with the disease, based on gonioscopic findings, but the condition of iridoschisis is not mentioned.

Aspirants for higher diplomas in ophthalmology should find the section on the pharmacology and clinical use of antiglaucomatous drugs particularly useful, as some textbooks of ocular physiology in the English language are insufficiently detailed on this subject. It is interesting to learn that the absorption of 120 ml. whisky promotes a fall in intraocular pressure lasting 4 to 5 hours. This should prove a popular remedy!

The surgical treatment of glaucoma is profusely illustrated in colour with emphasis on those procedures favoured by the author, such as iridosclerectomy *ab externo* (Foroni) for chronic simple glaucoma and thermo-sclerectomy (Scheie) for the chronic angle-closure type. The author does not give a definite answer to the controversial question of when (if at all) one should evacuate a choroidal detachment associated with a flat anterior chamber following filtering operations.

A chapter is devoted to cyclodialysis and goniotomy, and another to cyclodiathermy, with its modification of angiodiathermy as practised in Lyons. Brief reference is made to cyclocryotherapy. The final chapter covers some of the newer procedures, such as trabeculectomy, the sinusotomy of Krasnov, and a detailed description of the trabeculotomy of Harms with an appraisal of its indications.

The value of this excellent book would be enhanced by a much more comprehensive index and bibliography, and a few of the black and white photographs are lacking in contrast. There are one or two misprints but these are minor criticisms and the book can be thoroughly recommended.

Ophthalmology: Principles and Concepts. By FRANK W. NEWELL. 2nd ed., 1969. Pp. *x* + 527, 233 figs. Kimpton, London. (140*s.*)

The fact that a second edition of this work has proved necessary within 5 years of the publication of the first confirms our assessment of the original volume in these pages (*Brit. J. Ophthal.*, **50**, 555, 1966) and justifies the econiums then accorded to it.

It was recommended not to the average medical student—or rather not, to be more precise, to those following the curriculum at present in vogue in British medical schools, but to those with thoughts of taking up ophthalmology as a valuable introduction to their future life-work, to those doing junior House appointments in eye departments of general hospitals, or, indeed, of eye hospitals, to those in general practice who wish for a handy book of reference, and for eclectic reading to consultant physicians and neurologists.

This assessment still holds, in full. The new edition follows closely the pattern of the old, with some pruning, some re-writing, and improvement in many of the illustrations. A welcome, and unusual, feature is that, the format being the same, the new volume contains only 36 pages more than the old. Of these extra pages thirteen are devoted to a newly-introduced glossary of technical terms. This may well be welcome to our non-ophthalmological colleagues, to whom—we must admit—we are liable to write using esoteric definitions with which they may not be familiar.

This work continues to be, as it was first described, one of the better introductions to ophthalmology. The price increase of 48*s.* must, in a spirit of resignation if nothing else, be considered as very reasonable in these days, and it is a pleasure to record again that the production matches the high and consistent standards we have learned to expect from these publishers.

Adler's Textbook of Ophthalmology. By H. G. Scheie and D. M. Albert. 8th ed., 1969. Pp. 509, 565 figs. 38 col. pl. Saunders, Philadelphia and London. (£7 9*s.*)

On the retirement of the recent author, the eighth edition of Adler's *Textbook of Ophthalmology* has taken on an entirely new dress. It is edited by Harold Scheie and Daniel Albert, and six collaborating authors from the school at Philadelphia have contributed to it. To some extent, it is true, the personal nature of the old book is lost, for we all became accustomed to admire and respect Adler's opinion; but in other aspects it has gained and the editorship has been good. As before, its aim is to provide the medical student and practitioner with a concise working knowledge of the subject, but drastic changes have been introduced to meet the requirements of alterations in medical curricula in America and elsewhere which involve the curtailment of the time devoted to the many specialties in medicine to the benefit of a more complete philosophy; the arrangement is less topographical and the subject is approached from the point of view of the basic sciences and their medical implications.

A preliminary chapter on the terminology of the subject is followed by a second on anatomy. There are chapters on embryology and genetics, paediatric and medical and neuro-ophthalmology, glaucoma, ocular injuries, and the principles of ophthalmic surgery. Then follows an elaborate series of appendices, occupying more than 100 pages, on the symptomatology of ocular diseases, the clinical examination of the eye, its optical defects, its physiology, and the appropriate pharmacology. The entire book is thus different from its predecessors, completely re-written and re-illustrated. It is, in fact, difficult to understand why it is called Adler's textbook unless it is to retain the connection with the school of Philadelphia. However that may be, the result is interesting, the venture novel, and the book certainly deserves the widespread popularity attained by the previous editions.

Lighting and Seeing. By R. G. Hopkinson. 1969. Pp. *xi* + 120, figs. Heinemann, London. (35*s.*)

Seeing depends upon lighting, and without light no sight is possible. Perhaps the expert on vision has paid inadequate attention to lighting, and the lighting engineer has insufficiently studied vision. Whether this is so or not, it is clear that these two aspects have been developed independently. The purpose of this book is to further the attempts to provide a common basis for discussion of both vision and lighting. The author is a well-known writer on architectural lighting and daylighting and holds the chair of Environmental Design and Engineering at University College, London. This book is based on a course of lectures given to senior students of the human environment for the Diploma of Public Health, and for the Factory Inspectorate, but is stated to have been written with a wider readership in mind.

The first four chapters deal with the eye and vision, including binocular vision, colour vision, and the psychology of vision. This provides an interesting, lively, and not too academic approach for the novice. Then follows a bridging chapter on "Lighting and Vision" dealing with visual acuity, visual performance, and recommended levels of illumination. There are then five chapters giving a clear and concise outline of various aspects of lighting, including basic principles, natural and artificial lighting, glare, and arguments for and against fluorescent lighting as a substitute for natural light. The last chapter is concerned with statutory regulations regarding lighting in public buildings, factories, offices, and shops.

This book is welcome, since new works dealing with lighting appear only infrequently in Great Britain. It provides a very good basic introduction to vision and lighting and it is excellently conceived for the group for whom it was written. It could also be useful as an introductory treatise on lighting for students of ophthalmic optics, and on both vision and lighting for electrical engineers. It is, however, probably too elementary on both subjects for students of architecture, and the price is rather too high to recommend to them if such students would also need a more advanced text.

There are a few errors and inconsistencies which could be cleared up in a future edition. In spite of a general reluctance, the reviewer feels that all new books should be written only in metric units. It is confusing to have both English and metric units, and even the author gets tied up on page 27 when he states that 32 lux is approximately the illumination in a living room. Perhaps more seriously, although it is emphasised that seeing fundamentally involves the brain, the word "sensation" is often used when "perception" is implied. Less serious, but irritating, is to have "ophthalmologist" sometimes mis-spelt, and to have the photopic luminous efficiency of radiation curve misdrawn (Figure 6.1). Some of the diagrams too, have distracting arrows on them, and some, viewed in good lighting conditions, will be seen to be covered with a rash of little whiskers. It is not clear whether this is a subtle secret device for illustrating some hidden principle to students, or whether someone has just forgotten to rub out the construction lines.

The Cauterized Eye and Keratoplasty. (Das verätzte Auge und die Keratoplastik.) By A. Heinc. 1969. Pp. 91, 30 figs. Enke, Stuttgart. (*D.M.*20)

The treatment of the eye severely damaged by this type of injury is given in detail in this short monograph both in a long series of clinical cases, including recent and old leucomata, and in experimental work on rabbits. Lamellar keratoplasty is applicable to many of these unfortunate cases and the results are often excellent.

The Measurement of Colour. By W. D. Wright. 4th edition, 1969. Pp. 340, figs, refs. Hilger, London. (80*s.*)

It would be hard to overestimate the benefits to students, research workers, and industrial workers in colour, of the successive editions of Professor Wright's "Measurement of Colour" since its first appearance in 1944. Within one modest volume Wright gives a lucid exposition, from the beginning, of the basic principles of colorimetry, of the experimental techniques involved, and of the varied applications of colour measurement. To those—certainly including many ophthalmologists—who find the evaluation of colour by a mixture of mathematics and sensory concepts slightly mysterious, this book is particularly helpful, even for readers not specially interested in the minutiae of colour measurement. Trichromatic principles of course bulk largely but, well-established though they are, some changes of emphasis have occurred and these are reflected in two substantially new chapters of the present edition devoted respectively to "Metamerism" (the varying spectral compositions of stimuli in colour match) and "Colour Difference Metrology" (the coordination of least perceptible colour differences in different parts of the colour solid). Emendations and minor additions bring the text up-to-date throughout. This book is thoroughly recommended.

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Notes

Irish Ophthalmological Society

The Society's Prize, 1970

This award (value £50) is open to ophthalmic registrars working in Ireland. The successful candidate will be required to read a paper on the result of his work at the Annual Meeting of the Society in 1971, and the paper will be published with the Transactions of the Society.

Candidates should submit details of an ophthalmological project for report, research, or investigation, to be considered by the Council of the Society, *not later than April 1, 1970*, to the Hon. Sec., Irish Ophthalmological Society, 18, Fitzwilliam Place, Dublin 2.

University of Toronto

Department of Ophthalmology, Annual Meeting, May 6 to 8, 1970

A 3-day meeting will be held in Toronto on May 6 to 8, 1970. On May 6, there will be a Biochemistry Colloquium with guest speakers from Canada and the United States. The Twelfth Annual Research Meeting at which Dr. W. Noell will be the guest speaker will be held on May 7, and a clinical meeting is planned for May 8.

For further information write to Dr. P. K. Basu, Director of Ophthalmological Research, University of Toronto, 1 Spadina Crescent, Toronto 179, Canada.

Brooklyn Eye and Ear Hospital

Symposium, May 2, 1970

The Alumni Association announces a one-day symposium on the surgery of congenital eye disorders to be held at the Granada Hotel, Brooklyn, N.Y., on May 2, 1970. Further information may be obtained from the Hospital, 20 Greene Avenue, Brooklyn, N.Y. 11238, U.S.A.

Austrian Ophthalmological Society

Annual Meeting, June 4 to 7, 1970

The 13th Annual Meeting of the Austrian Ophthalmological Society will take place on June 4 to 7, 1970. Those interested should write to the Secretary, 13. Jahreshauptversammlung der Österreichischen, Ophthalmologischen Gesellschaft, Wiener Medizinische Akademie fur arztliche Fortbildung, Alserstrasse 4, A-1090 Wien, Osterreich.

Society of Eye Surgeons

The International Eye Foundation is pleased to announce the formation of the Society of Eye Surgeons to promote the science of ophthalmic surgery among all peoples and nations.

Qualified ocular surgeons should write for information and application forms to J. H. King, Jr., M.D., Director, The Society of Eye Surgeons, 5255 Loughborough Road, N.W., Washington, D.C., U.S.A , 20016.

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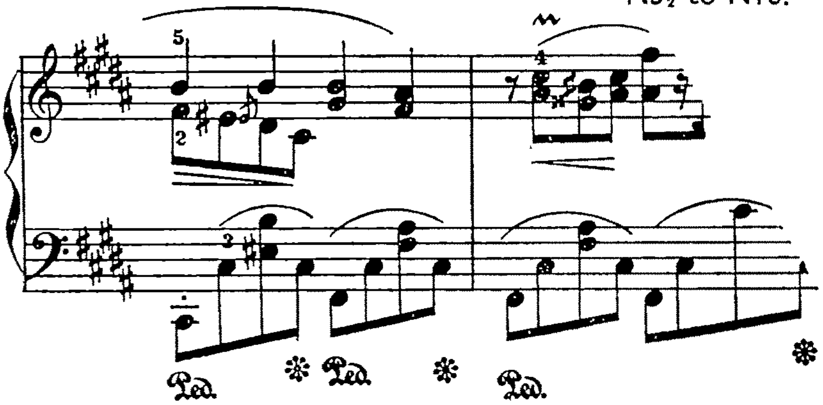

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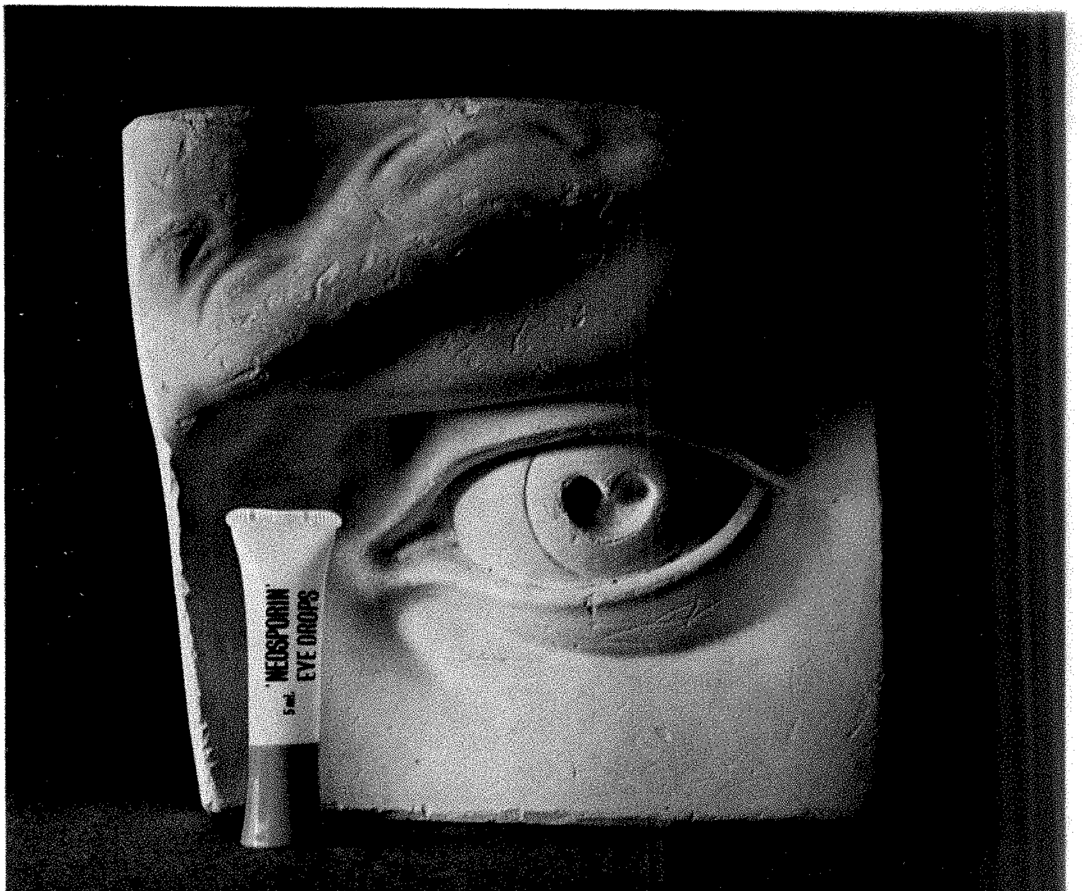

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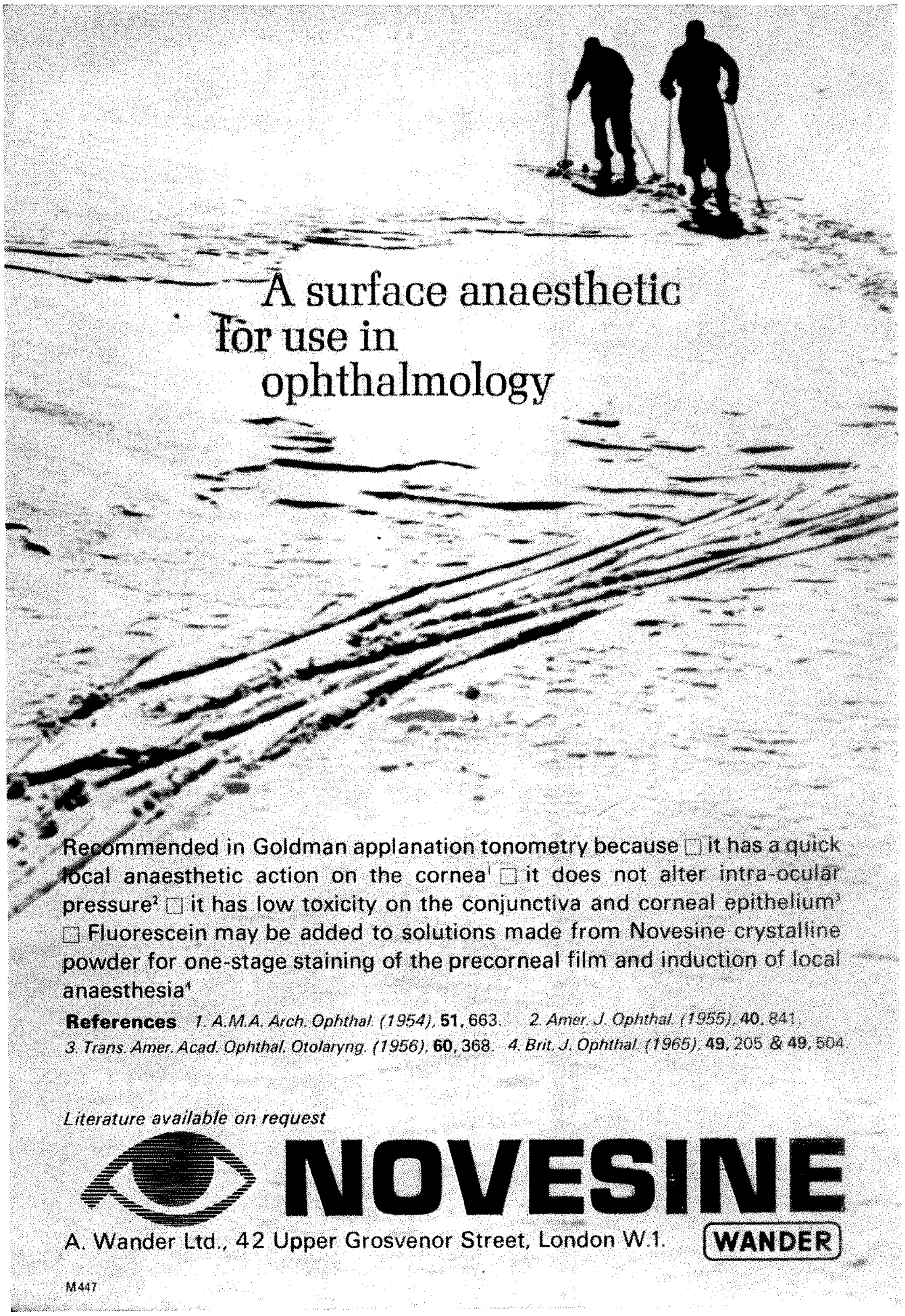

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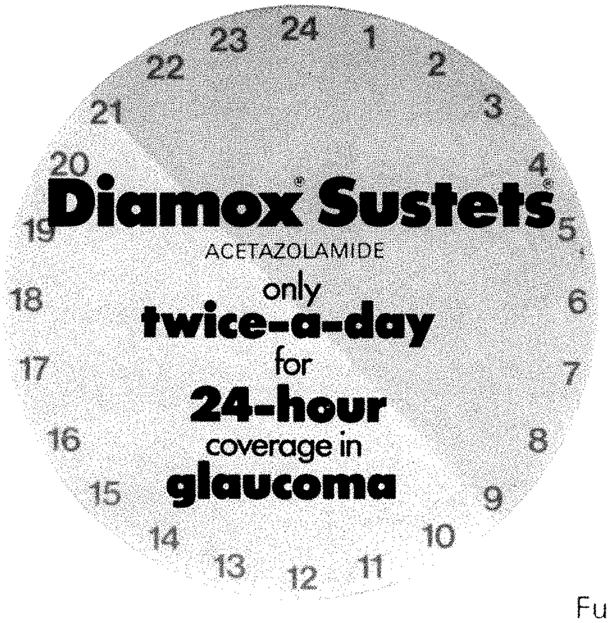

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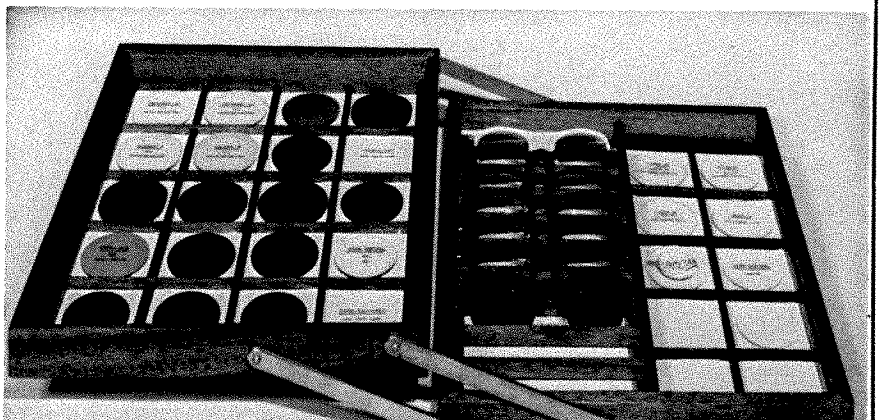

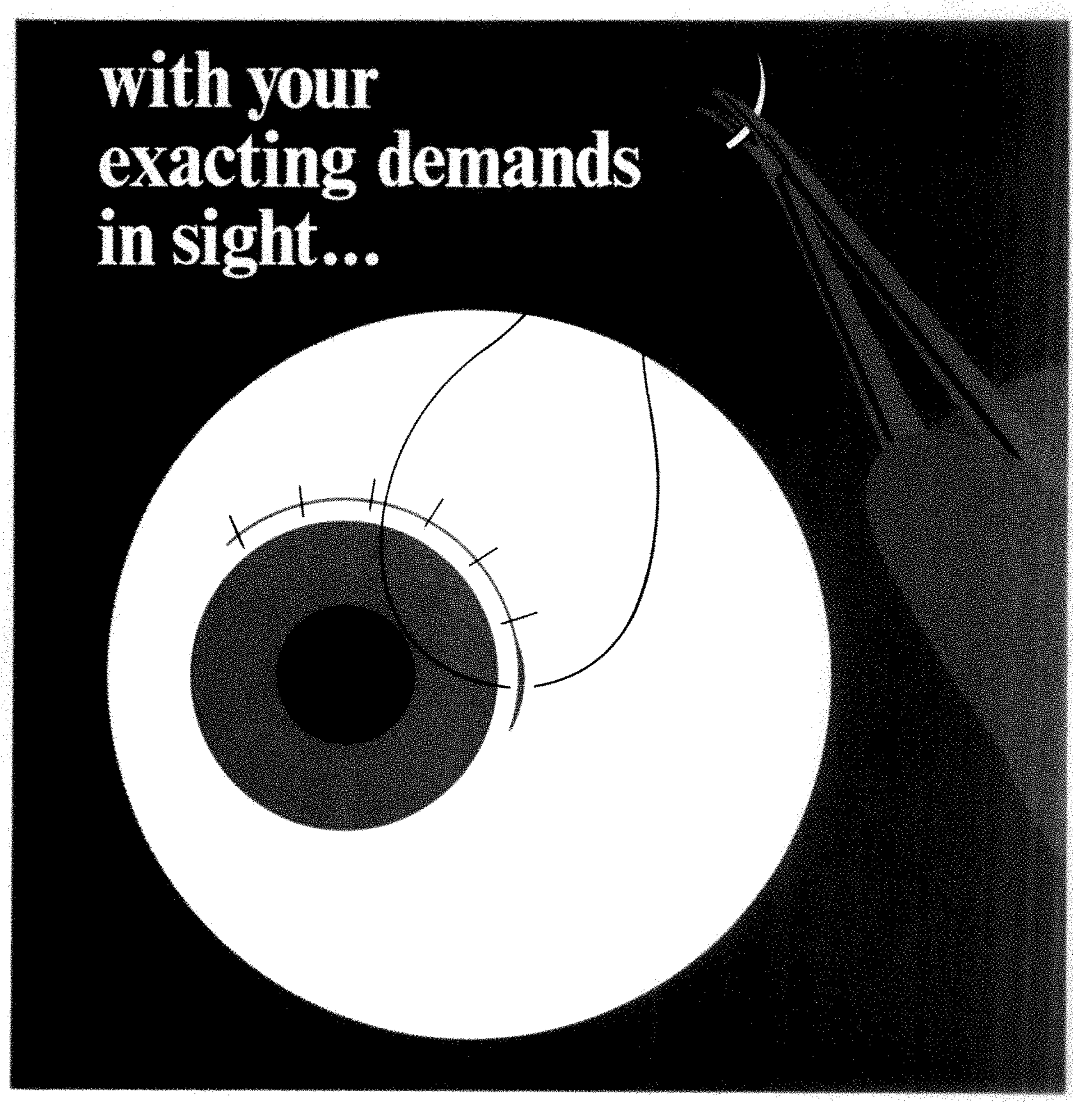

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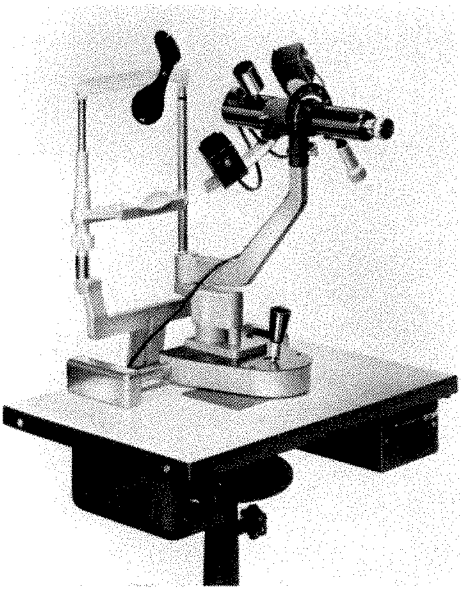

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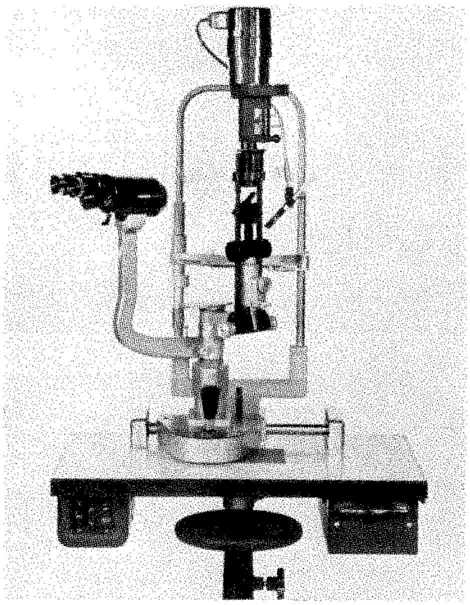

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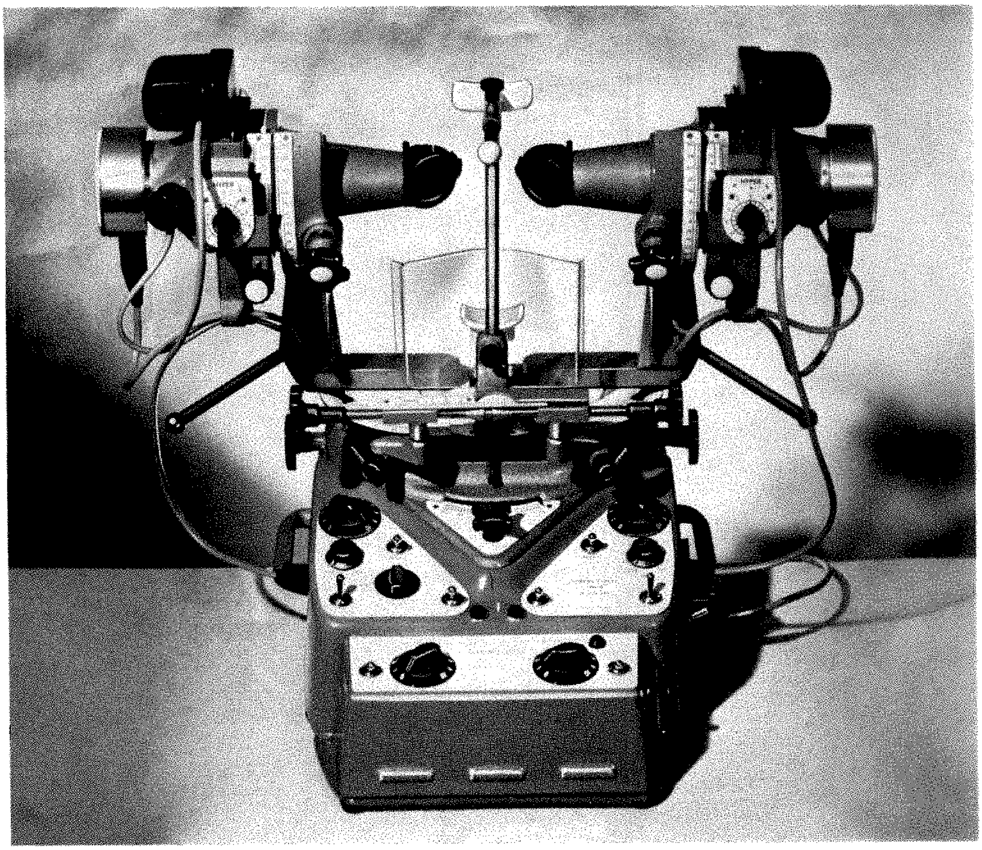

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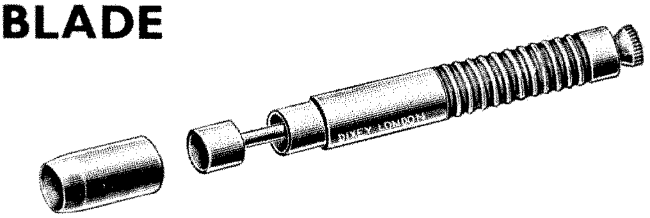

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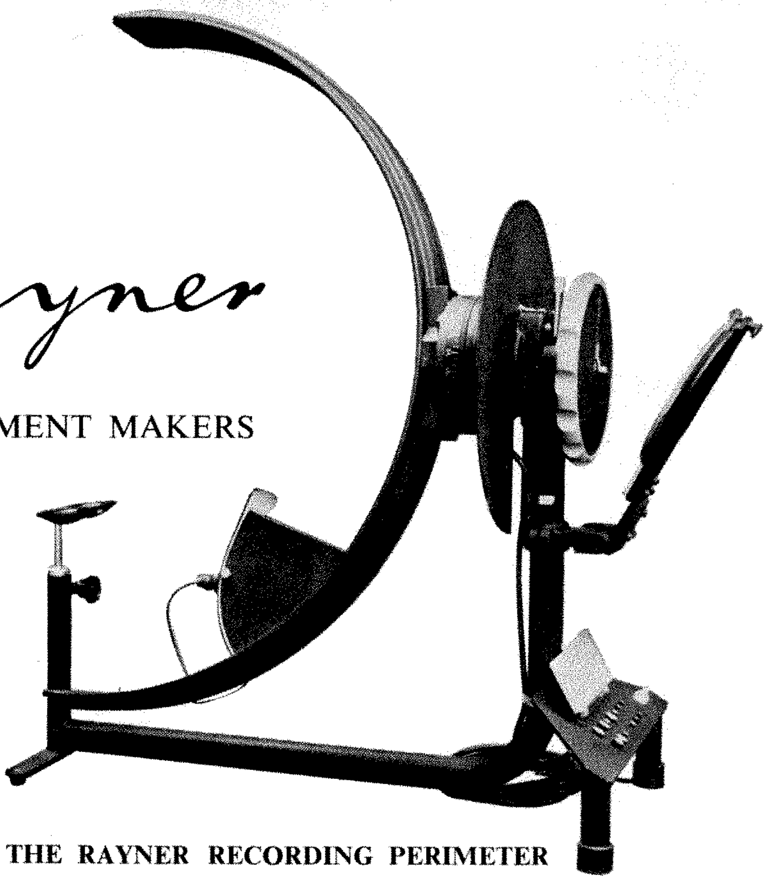

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Communications

Assessment of established cases of chronic simple glaucoma

R. F. FISHER*, R. G. CARPENTER, AND C. WHEELER

Institute of Ophthalmology, University of London

Since tonography was first introduced by Grant (1950), patients with chronic simple glaucoma have repeatedly been shown to have a marked reduction in outflow facility (Kronfeld, 1961). Impaired outflow has also been correlated with changes in the structure and patency of the trabecular meshwork (Teng, Paton, and Katzin, 1955; Yamashita, Becker, and Cibis, 1960). This confirmed the view that impaired outflow facility, together with cupping of the disc and loss of the field, were constant characteristics of the glaucomatous eye (Becker and Shaffer, 1961). The present study was therefore undertaken in proven cases of chronic simple glaucoma, as indicated by cupping of the disc and loss of the field, firstly to discover if impaired outflow facility were a better measure of the degree of glaucoma than raised intraocular pressure and, secondly, to see if it were possible to predict the loss of field from the impaired outflow facility.

Material and methods

In the course of 18 months, 400 patients with proven open-angle chronic simple glaucoma presented for treatment and from these patients 33 (fifty eyes) were chosen for this survey. Two factors account for this low rate of selection:

(1) Only patients who had received no previous treatment were included;

(2) Of these patients only a few fulfilled the stringent criteria for field testing (Fisher, 1968).

To obtain a full range of cases a few apparently normal eyes of patients with undoubted chronic simple glaucoma in the other eye were included. All eyes were subjected to a general ophthalmological examination, which included gonioscopy.

FIELD ESTIMATION

The method of selection and examination of the visual fields has been described previously (Fisher, 1968). In this study all quadrants of the field were examined separately in a Goldmann perimeter, with a target of 4 mm.^{2} and of brightness 45 apostilbs. This target was used since the diagnosis was not in question and only definite and permanent field defects were ascertained. Furthermore, a target of this size and luminosity gives an average field, extending about 45° in the nasal quadrant, and nose and brow obstruction is usually absent (Fisher, 1967). The centripetal and centrifugal fields were repeated on two separate occasions, and if discrepancies greater than 5° per quadrant were found the patient was excluded from the study.

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Address for reprints. R. F. Fisher, Institute of Ophthalmology, Judd Street, London, W C 1

For the purpose of computer analysis, the loss of field of each patient was corrected for the normal senile decrease in the size of the field. This correction was made as follows: after the size of the field in each quadrant had been measured, the average size of the field per quadrant in normal subjects of the same age was obtained from published tables (Fisher, 1968). The difference between these two values was taken as the corrected loss of field.

TONOMETRY AND TONOGRAPHY

Intraocular pressures were recorded by applanation tonometry, using the Haag-Streit 900 slit lamp, and tonography was performed with the Schwarzer electronic tonometer with recorder. Each patient was examined on three occasions by tonometry and tonography. The time of examination was arranged at three successive visits for about 9–10 a.m., then 1.30–2 p.m., and finally 4.30–5 p.m. Tonography results were obtained by the rigidity-corrected graphic method of Moses and Becker (1958).

ESTIMATION OF CUPPING OF THE DISC

The estimation of the cupping of the disc, which was performed by one of us (R.F.F.) before any other investigations, was graded into six groups normal, doubtful, and four grades of glaucomatous cupping of increasing severity, as suggested by Becker and Shaffer (1961).

SIZE OF THE PUPIL

This was an average value of eight estimations during the two field tests taken 5 minutes after the eye had been light-adapted to a standard background illumination of 45 apostilbs.

ANALYSIS OF RESULTS

The data were transferred to punched cards for computer analysis by one of us (R.G.C.). A preliminary analysis was carried out with a BMD computer programme (Dixon, 1966). The correlation of each pair of variables was computed and most of the relationships plotted. Finally a multiple regression analysis, using the method of Rushton (1951), was undertaken to ascertain the best predictors of field-loss in each of the four quadrants.

Results

One of the most important observations in this study is the close relationship between the state of the disc and the size of the field. The correlation between these variables is so great that it is possible to relate them in three of the four field quadrants by linear or quadratic equations. This means that the recording of individual results in the form of a Table becomes unnecessary and this has therefore been omitted.

Fig. 1 shows these relationships. It will be seen that the upper nasal field shows a rapid linear or proportionate loss and this can be represented by the equation:

(a) $F = 45{\cdot}9 - 8{\cdot}4\ D$,

where F = size of field in degrees

D = numerical coefficient of cupping of the disc.

The lower nasal and upper temporal quadrants show a more gradual loss; represented by the quadratic equations:

(b) $F = 47 - 1{\cdot}6\ D^2$

(c) $F = 46 + 4{\cdot}7\ D - 2{\cdot}5\ D^2$.

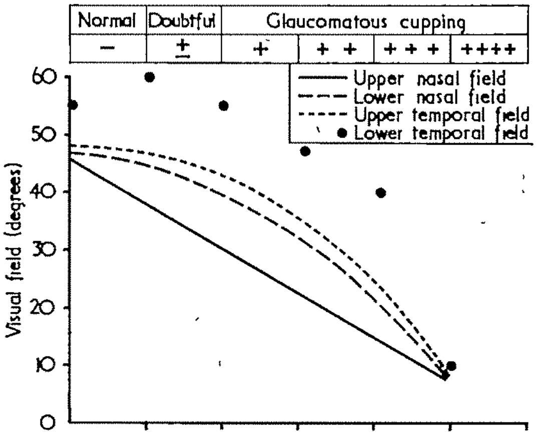

FIG. 1 *Relationship between state of disc and size of field for each quadrant of the visual field*

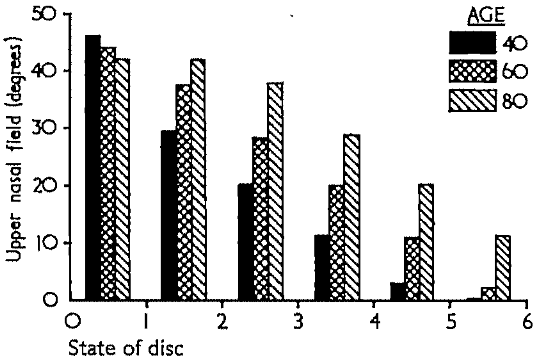

FIG. 2 *Significance of glaucomatous cupping in relation to upper nasal loss of the visual field and age*

Note The normal values are taken from a normal group of 105 eyes (Fisher, 1968)

The lower temporal field loss cannot be completely described by a quadratic curve since it occurs too late in the disease. It is therefore shown as a series of points corresponding to the average loss for each state of the disc.

All the other observations show much less significant relationships with each other and can therefore be expressed only by a single correlation coefficient. Table I (*see* p. 220) shows these correlations between age, pupil, field quadrants, pressure range, facility outflow, facility range, and state of the disc.

As mentioned previously, the correlation between the state of the disc and the size of the field is greater than that between any other pair of variables, apart from the correlations between field quadrants. It is disappointing to find that the complex objective assessment of outflow facility is less closely correlated with the reduced size of the field than the simple subjective and inexact assessment of the cupping of the disc. Furthermore, inspection of the plots of the relationships between size of field and average pressure, and of size of field and average outflow facility, does not suggest that these lower correlations are due to the relationships' being non-linear. These lower correlations indicate, therefore, that the size of the field is better assessed by inspection of the disc than by measurement of either pressure or outflow facility.

Discussion

A well-established case of chronic simple glaucoma has the characteristic clinical features of excavation of the optic nerve head, raised intraocular pressure, and typical field defects.

Table I *Correlation between characteristics of fifty glaucomatous eyes*

Characteristics	*Age (yrs)*	*Pupil size*	*Upper nasal field*	*Lower nasal field*	*Upper temporal field*	*Lower temporal field*	*Average pressure*	*Pressure variation*	*Average outflow facility*	*Outflow facility variation*	*State of the disc*
Age (yrs)	1·000	—0·414‡	0·143	0·004	—0·112	—0·110	0·090	0·194	0·314	0·034	0·163
Pupillary size	—0·414‡	1·000	—0·155	—0·096	—0·125	—0·120	—0·245	—0·409‡	—0·055	—0·304†	—0·051
Upper nasal field	0·143	—0·155	1·000	0·751*	0·792*	0·621*	—0·501*	—0·241	0·452*	0·214	—0·780*
Lower nasal field	0·004	—0·096	0·751*	1·000	0·754*	0·866*	—0·511*	—0·378‡	0·452*	0·314†	—0·769*
Upper temporal field	—0·112	—0·125	0·792*	0·754*	1·000	0·777*	—0·482*	—0·316†	0·235	0·233	—0·743*
Lower temporal field	—0·110	—0·120	0·621*	0·866*	0·777*	1·000	—0·420‡	—0·311†	0·277	0·307†	—0·645*
Average pressure	0·090	—0·245	—0·501*	—0·511*	—0·482‡	—0·420‡	1·000	0·592*	—0·588*	—0·240	0·567*
Pressure variation	0·194	—0·409‡	—0·241	—0·378‡	—0·316†	—0·311†	0·592*	1·000	—0·222	0·065	0·315†
Average outflow facility	0·314†	0·055	0·452*	0·452*	0·235	0·277	—0·588*	—0·222	1·000	0·304†	—0·466*
Outflow facility variation	0·034	—0·304†	0·214	0·314†	0·233	0·307†	—0·240	0·065	0·305†	1·000	—0·145
State of the disc	0·163	—0·051	—0·780*	—0·769*	—0·743*	—0·645*	0·567*	0·315†	—0·466*	—0·145	1·000

P < 0·05	Correlation = 0·279
P < 0·025	Correlation = 0·317
P < 0·01	Correlation = 0·361
P < 0·001	Correlation = 0·451

† Correlation is significant 0·05 > P > 0·01

‡ Correlation is significant 0·01 > P > 0·001

* Correlation is significant 0·001 > P

A common defect is peripheral loss in the upper nasal field. Nearly a century ago, Schmidt (1877) suggested that selective impairment of circulation in the lower temporal portion of the retina was the cause. Recently it has been found that after the age of 60, even in normal subjects, loss occurs in the upper nasal field quadrant (Fisher, 1968). Even when, as in the present study, this senile loss is taken into account, there is still, with early cupping of the disc, a selective loss of field in this quadrant.

CHANGES IN THE UPPER NASAL FIELD WITH AGE AND CUPPING OF THE DISC

The influence of age upon the extent of loss of field, resulting from a given degree of cupping of the disc, was found in the present data to be related by the equation:

$$F = 21{\cdot}2 - 8{\cdot}9\,D + 0{\cdot}42\,A$$

where A = age of patient in years,
D = numerical coefficient of disc cupping,
F = size of field in degrees.

The last term of this equation, representing the age of the patient, is additive. This implies that the loss of the field for a given degree of glaucomatous cupping is less pronounced the greater the age of the patient. Although appearing to conflict with the previous finding, that the loss of field occurs as an ageing process even in normal subjects, it merely shows that glaucomatous cupping of the disc in this age group causes a smaller amount of loss of field.

This is shown graphically in Fig. 2 (*see* p. 219) for the selected ages of 40, 60, and 80 years. A moderate degree of disc cupping (++) at the age of 40 years causes a field loss of 75 per cent., while the same degree of cupping for the ages of 60 and 80 years causes field losses of 45 per cent. and 15 per cent. respectively. This equation, therefore, gives a precise indication of the seriousness of the cupping of the disc in young patients. Conversely, the elderly patient, with a markedly cupped disc, may only have a slight or moderate loss in the upper nasal field.

CORRELATION BETWEEN STATE OF THE DISC AND SIZE OF THE FIELD

The analysis described in the Appendix has confirmed that in the glaucomatous eye:

(a) Field defects and cupping of the disc are the most stable characteristics.
(b) There is a selective and early progressive impairment of the upper nasal field.
(c) There is later and slower loss of field in the upper temporal and lower nasal fields.
(d) There is late but eventually rapid impairment of the lower temporal field.
(e) Subsidiary measurements, such as pressure and outflow facility, do not have any importance in modifying an estimation of the loss of field from the appearance of the disc.

Thus the view of Graham and Hollows (1966) is confirmed, that, despite the difficulty of grading changes at the disc, ophthalmoscopy is the best method of detecting positive cases of simple glaucoma.

CORRELATION BETWEEN LOSS OF FIELD, INTRAOCULAR PRESSURE, AND OUTFLOW FACILITY

Table I shows that overt cases of chronic simple glaucoma have a reduced size of the visual field which tends to correlate more closely with mean raised intraocular pressure than with mean reduced outflow facility. The upper nasal field very significantly correlates with both values (Pressure $r = -0{\cdot}501$; outflow facility $r = 0{\cdot}452$; in both cases $0{\cdot}001 > P$).

These correlations are shown graphically in Figs 3 and 4. Table I also shows that mean outflow facility correlates very significantly with intraocular pressure ($r = -0{\cdot}588$; $P < 0{\cdot}001$). This correlation illustrates the well-established dependence of raised pressure upon low outflow facility.

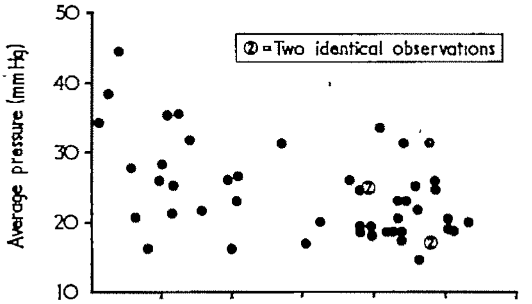

FIG. 3 *Correlation between average pressure (three determinations) and average upper nasal field (two estimations)*

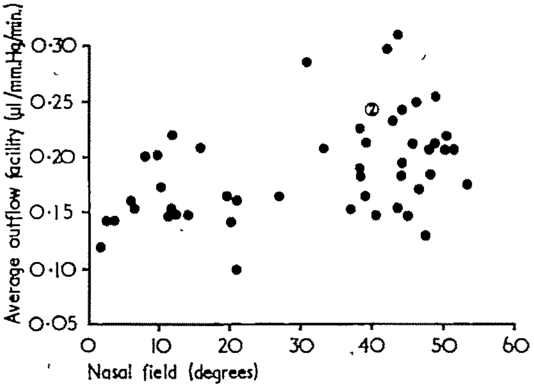

FIG. 4 *Correlation between average outflow facility (three determinations) and average upper nasal field (two estimations)*

The value of tonography compared with pressure estimations in assessing the glaucomatous state must now be considered. This consideration involves the definition of the "degree of glaucoma" as a decrease in the size of the field, and, secondly, using the average values of three outflow facility measurements and three intraocular pressure readings, recorded together on separate occasions throughout the day for correlating in turn with the size of the field. When this was done, the complex technique of tonography was of less value in assessing glaucoma than the simple measurement of the intraocular pressure. Furthermore, the partial correlations between size of field and average outflow facility, when pressure is held constant, are insignificant for each field (Table VI, *see* p. 228). Thus tonography provides no information about the "degree of glaucoma" not given by tonometry. This view so contradicts much of current thought in regard to the value of tonography as an estimate of the glaucomatous state that it must be discussed in detail. These findings could be due to (*a*) imperfections of tonographic technique in the present study; or to an incorrect view regarding (*b*) the calculation of outflow facility; or (*c*) the constancy of outflow facility values compared with pressure readings.

(*a*) *Tonographic technique*

It could well be argued that poor tonographic technique resulted in the low correlation of outflow facility with glaucomatous field size. Since, however, tonography was repeated three times in every eye, it is easy to compare the variations obtained with those found by other workers. Gloster (1966) suggested that the variation in tonography was about 20 per cent. above or below the mean value. In this series the mean value is 0·19 µl./mm.

Hg/min., the mean range 0·05 µl., and the average variation for a single reading 26 per cent. Becker and Shaffer (1961) gave the standard deviation for a normal population as ±0·05 µl. In this series, where outflow facility values are reduced, the standard deviation was plus or minus 0·036 µl. The variations found in this study do not therefore differ from those found by others, and, in addition, all the tonographies were performed by one person (C.W.) using the same instrument.

(*b*) *Outflow facility measurement*

Tonography was introduced to give a stable and reproducible numerical coefficient for the rate of flow of aqueous per mm. Hg pressure, through the outflow channels of the eye. Some of the basic assumptions have been critically reviewed on many occasions, for example by Kronfeld (1961). One assumption, namely the uniformity of blood flow through the choroidal vasculature, has been shown to be reasonably constant by radioactive plasma or labelled red blood cell studies. It is little appreciated, however, that slight variations in choroidal thickness, quite outside the accuracy of present methods of estimating the blood flow, can cause profound variations in the intraocular volume. For example, if the choroid increased by only 2 µ—the thickness of a single red blood cell—during a tonographic estimation of 4 minutes' duration, the measurement of outflow facility would be underestimated by about 75 per cent. in an eye with moderately advanced glaucoma.

A further assumption, that outflow facility is independent of intraocular pressure, has been used to calculate changes in the properties of the trabecular meshwork (McEwen, 1958). These calculations presupposed the constant calibre of the outflow channels but Clausen and Harris (1965) have shown that the outflow facility in the cat can be altered by a raised intraocular pressure. It was found in this study that tonography performed at different times during the day was more variable than pressure, the individual variation being 27 per cent. for tonography and 16 per cent. for pressure. Variations in tonographic values in normal and glaucomatous eyes throughout the day have also been reported previously (Newell and Krill, 1965; Berry, Drance, and Wiggins, 1967).

Indeed, when average values for outflow facility, together with average measurements of intraocular pressure, were compared with the size of the field, the degree of glaucoma was less closely correlated with outflow facility (Table I). One is forced, therefore, to conclude that, if tonographic assumptions are correct even in the glaucomatous eye, outflow channels still have large diurnal changes in resistance. These changes in resistance, like variations in pressure, adversely affect the correlation between outflow facility and decreasing size of field.

(*c*) *Constancy of outflow facility and pressure*

If it could be shown that tonographic and pressure variations correlated to a similar degree with autonomic ocular tonus, then changes in outflow facility, like those in pressure, could be attributed not to defects in technique or methods of calculation but to true alterations in outflow resistance. Much work has been done on the relationship between nervous activity and intraocular pressure and, to a lesser extent, on outflow facility; but the precise importance of the ocular autonomic nerve supply is still a matter of speculation (Schmerl and Steinberg, 1949; Gloster and Greaves, 1957). Fortunately, an indication of the balance between the parasympathetic and sympathetic activity of the eye may be deduced from the size of the pupil.

Do changes in outflow vary significantly with the size of the pupil? If they do not, then it is a stable characteristic of the glaucomatous eye, like cupping of the disc and loss of field. It should be noted, from Table I, that the size of field in this glaucomatous population and the state of the disc have non-significant correlations with pupillary size. If outflow facility variation does indeed correlate with pupillary size, it is, like raised pressure, only another labile characteristic of the glaucomatous state.

In the present study the size of the pupil was shown to have a significant negative correlation with both pressure (P less than 0·01: Table I) and with outflow facility (P less than 0·05: Figs 5 and 6). All other variables, apart from age, showed no significant correlation with pupillary size. It is well established that the pupil decreases in size with age (Birren, Casperson, and Botwinick, 1950) and a survey of normal cases under the same conditions of illumination showed an even more significant correlation with age ($r = 0{\cdot}701$) over an extended age range (15 to 81 years) (Fisher, 1968). However, even if the significant effect of age in pupillary size is allowed for, by a calculation of the partial coefficients of pressure variation and outflow facility variation with pupillary size, the latter values still remain significant (pressure variation $r = -0{\cdot}369$; outflow facility variation $r = -0{\cdot}318$).

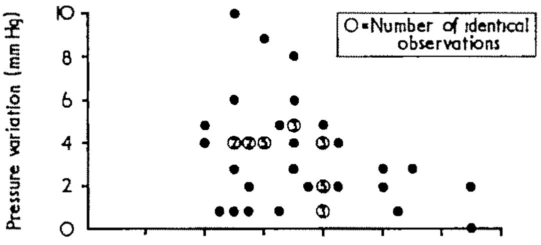

FIG. 5 *Correlation between each subject's variation in pressure (three determinations) and mean pupillary size (eight determinations)*

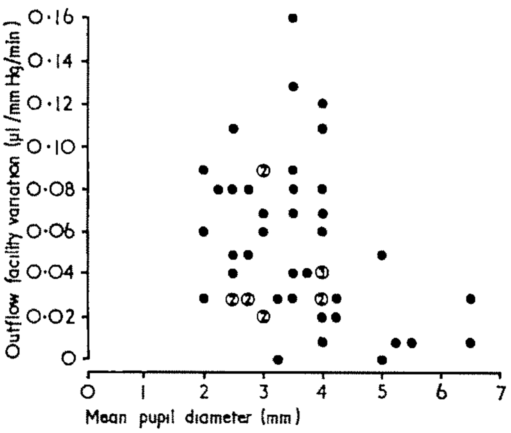

FIG. 6 *Correlation between each subject's variations in outflow facility (three determinations) and mean pupillary size (eight determinations)*

Törnqvist (1967) had shown that in the primate eye the parasympathetic probably plays the predominant role in miosis and accommodation, so that the smaller the pupil the greater the parasympathetic tonus. If this is so, increased parasympathetic tonus would automatically lead to the possibility of greater change if it were inhibited. This, in turn, would be reflected in pupillary miosis, correlating with large pressure and outflow variations. For example, from Figs 5 and 6, with a pupillary size of 2 mm., outflow facility variation is 0·08 µl. and pressure variation is 5·0 mm. Hg, while with a pupillary size of 5 mm., outflow facility varies only by 0·035 µl. and pressure only by 1·5 mm. Hg.

Duke-Elder (1957) expressed the view that the secret of this disease could not be entirely expressed in terms of mathematical formulae, and it would seem that the careful measurement of outflow facility in this study supports this view. Until we can evolve better methods of studying the degree of cupping of the optic nerve head, and forecasting its resistance to raised intraocular pressure, further refinements of tonographic techniques are unlikely to yield more useful information in the management of simple glaucoma.

Summary

A statistical correlation between the various characteristics of fifty glaucomatous eyes has shown that simple subjective assessment of cupping of the disc correlated more closely with the decrease in the size of the visual field than with either intraocular pressure or outflow facility. Furthermore, when the averages of pressure and outflow facility were separately correlated with mean quadratic size of field, average pressure readings correlated more closely than average outflow facility values. Since variations in pressure in individual subjects and in outflow facility also correlated significantly with the size of the pupil, it was concluded that reduced outflow facility was no more a stable property of the glaucomatous eye than raised intraocular pressure.

We are indebted to Mr. Redmond Smith for the facilities to examine patients referred to the Glaucoma Clinics of Moorfields Eye Hospital, and to the Imperial College computing centre and the Cambridge mathematical laboratory for the use of their computers for this analysis.

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Appendix

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The multiple regression analysis

We looked for the best predictor of size of field among the following variables:

(1) Age
(2) Sex
(3) Pupillary size
(4) Average pressure of three readings
(5) Range of pressure readings
(6) Average outflow facility of three estimates
(7) State of the disc, D, recorded on a sixpoint scale.

Scatter diagrams showing the relationships between the size of the field and the first six variables did not suggest that they were non-linear, but the relationships between the size of the field and state of the disc were obviously not linear for some fields. The mean loss of field corresponding to each of the five abnormal states of the disc can be completely represented by the regression of size of the field on D, D^2, and three other constants. The relationship between the size of the field with each of these terms was considered.

Table II shows the partial correlations between the size of the field and each of the other variables after removing the contributory state of the disc, *i.e.*, these correlations are the average correlations between the size of the field and age, pupillary size, pressure, etc., within a given state of the disc.

Table II *Partial correlations after taking account of correlation, size of field, and state of disc*

Variable	*Upper nasal*	*Lower nasal*	*Upper temporal*	*Lower temporal*
Age (yrs)	0·438‡	0·205	0·015	−0·007
Pupillary size	−0·311†	−0·212	−0·243	−0·200
Pressure	−0·115	−0·143	−0·110	−0·087
Pressure range	0·007	−0·224	−0·130	−0·149
Outflow	0·160	0·166	−0·187	−0·035
Outflow range	0·164	0·320†	0·189	0·283

Significance levels

$r > 0{\cdot}282$	$0{\cdot}05 > P$	indicated by †
$r > 0{\cdot}365$	$0{\cdot}01 > P$	indicated by ‡
$r > 0{\cdot}455$	$0{\cdot}001 > P$	indicated by *

The probability of observing a correlation with module larger than 0·438 is <0·0016. Hence the probability of observing one such correlation in 24 is <0·039.

Table III (opposite) shows that all these correlations are small and that only four are statistically significant—three at the 5 per cent. level and one at the 1 per cent. level. Among 24 correlations these might easily exceed the 5 per cent. level by chance, but the probability of a single partial correlation exceeding 0 438 by chance is less than 0·16 per cent., and so the chance of observing one correlation as large as this among 24 is less than 4 per cent. Thus it is concluded that the partial correlation between age and loss of the upper nasal field is statistically significant

Table III shows the analysis of variance when the size of the upper nasal field was regressed on the state of the disc after the first six variables. This shows that the state of the disc provides information about the size of the field that is not contained in any of the other observations. It also shows that, for the upper nasal field, the relationship between the state of the disc and the size of the field is fully described by a straight line.

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Table III *Analysis of effect of state of disc after six other variables on size of upper nasal field corrected for age*

Source of variation		*Sum of squares*	*Degrees of freedom*	*Mean square*	*Variance ratio*	*Significance*
Average pressure		3273·3	1	3273·3	35·33	Cannot be validly tested because of significant effect below
Average outflow facility after average pressure		490·0	1	490·0	5·29	
Pupillary size		922·1	1	922·1	9·95	
Age (yrs)		0·6	1	0·6	0·01	
Sex		87·3	1	87·3	0·94	
Pressure range		59·7	1	59·7	0·64	
Outflow facility range	after factors above	45·4	1	45·4	0·49	
State of disc						
Coeff. of D		4408·1	1	4408·1	47·58	0·001 > P
Coeff. of D^2		166·9	1	166·9	1·80	Insignificant
3 constants		144·8	3	48·3	0·52	Insignificant
Residual		3428·1	37	92·7		
Total		13026·3	49			

Table IV presents the analysis of variance when the size of the upper nasal field is regressed first on the state of the disc, treated as a linear variable, and then on each of the other variables in succession. Of these, besides the state of the disc, age is the only other significant variable in the regression.

Table IV *Analysis of effect of six variables after state of disc on size of upper nasal field, corrected for age*

Source of variation		*Sum of squares*	*Degrees of freedom*	*Mean square*	*Variance ratio*	*Significance*
State of disc—Coeff. of D		7923·5	1	7923·5	86·87	—
Age (yrs) after state of disc		977·0	1	977·0	10·71	0·01 > P > 0·001
Sex		17·1	1	17·1	0·19	Insignificant
Average pressure		78·6	1	78·6	0·86	Insignificant
Average outflow facility	after factors	56·3	1	56·3	0·61	Insignificant
Pupillary size	above	202·1	1	202·1	2·22	Insignificant
Pressure range		17·2	1	17·2	0·19	Insignificant
Outflow facility range		14·6	1	14·6	0·14	Insignificant
Residual		3739·8	41	91·2		
Total		13026·3				

Similar multiple regression analyses were carried out for each of the other fields. For the lower nasal field both D and D^2 were significant, but neither the range of outflow facility nor any of the other variables is significant after regressing on D and D^2. The size of the upper temporal field is highly correlated with the state of the disc, and the relationship can be fully described by the quadratic term D^2. In addition, average outflow facility is also just significant for upper temporal field, the partial correlation being −0·295; 0·05 > P > 0·01.

The relationship between the lower temporal size of the field and the state of the disc can be fully described only by fitting a constant for each state of the disc. After fitting these constants, no other variable by itself is significant, but a constellation of four variables was found which together were significant at the 5 per cent. level. These four variables were sex, average pressure, range of pressure, and range of outflow facility. There was no obvious explanation why a linear combination of these four variables should predict the size of the lower temporal field.

Thus, for all four fields, after taking account of the highly significant effect of the state of the disc, only marginally significant relationships were found, apart from a highly significant effect of age on size of the upper nasal field. These marginally significant relationships are probably due to the large number of relationships that have been examined, and we regard them as fortuitous. The regression equations found in these analyses are given in Table V.

Table V *Coefficients of significant variables, with standard errors, for predicting size of field in degrees*
Residual standard deviation of size of field also shown in degrees

Field	*Coefficient of*		*Constant*	*Residual SD*
Upper nasal[1]	D −8·28 ± 0·89	Age (yrs) 0·582 ± 0·179	14·8	9·6
Lower nasal[2]	D 4·70 ± 2·08	D^2 −2·53 ± 0 44	46·0	6·9
Upper temporal[2]	D^2 1·57 ± 0·17		41·7	8 9
Lower temporal[2]	Constants corresponding to state of disc 0 +− + ++ +++ ++++ 61·1 63·3 61·1 55·9 48·6 9 3			7·0

[1] Corrected for age
[2] Uncorrected for age

Table VI shows the partial correlations between the size of the field, for all four fields, and outflow facility when pressure is held constant. All these partial correlations are small and none is statistically significant; $P > 0·1$ in each case. This shows that the estimate of average outflow facility provides no information as to loss of field that is not given by an estimate of average pressure.

Table VI *Partial correlations between size of field and outflow facility when pressure is held constant*

Variable	*Field*			
	Upper nasal	*Lower nasal*	*Upper temporal*	*Lower temporal*
Outflow facility	0·22	0·22	−0 07	0 04

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Fluorescence angiography of the iris

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Jensen and Lundbaek (1968) reported a technique of fluorescence iris angiography using a lens of 20 cm. focal length placed in front of the Zeiss fundus camera.

This technique, though attractive in its simplicity, has certain disadvantages, *i.e.* the image size of 24 × 24 mm. and distortion at the margins of the image. Furthermore it is necessary to use the maximum flash intensity (this requires a flash frequency of one per 1·5 — 2 sec.) and the high-speed films that must be used give course-grained pictures.

Bruun-Jensen (1969) and Baggesen (1969) reported a method of iris fluorescence angiography using a modified Zeiss photo slit lamp. This solves the problem of image size, in this case 24 × 36 mm. without marginal distortion. Certain modifications were deemed necessary, i.e. air-cooling of the flash-bulb and the fitting of a concave lens with a blue filter in front of the slit. Again a high-speed film was used, which required forced development.

A relatively simple and cheap technique of iris angiography is described below, in which a Zeiss fundus camera is used with an external motorized Nikon camera (Fig. 1).

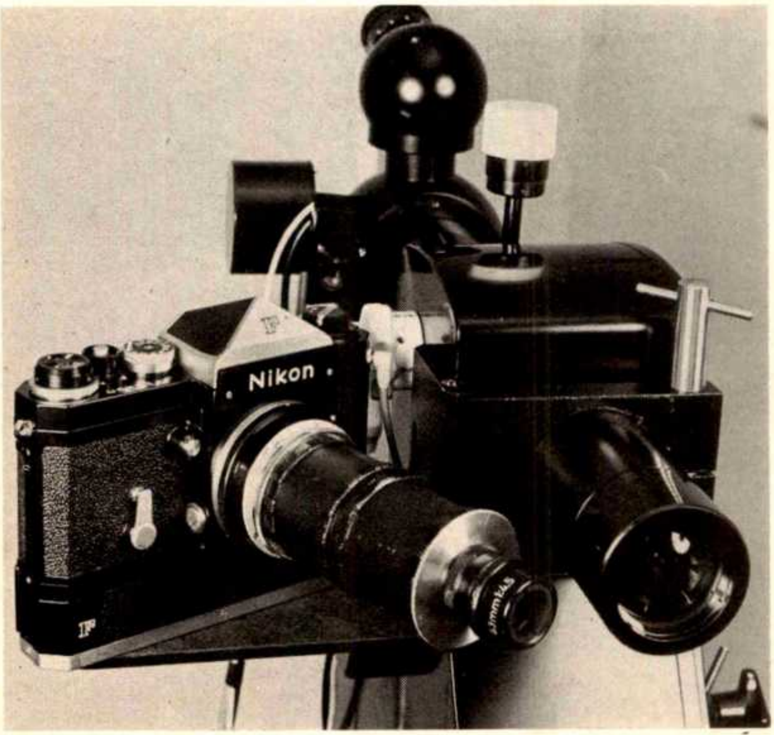

FIG. 1 *Attachment of motorized Nikon camera to Zeiss fundus camera.*

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Method

A modified Zeiss fundus camera is used, with a built-in Baird Atomic B4 interference filter, to supply the blue excitation light. A motorized Nikon camera F 36 was attached to the side of the fundus camera (Fig. 1). This Nikon camera was fitted with an extension ring set containing the yellow Schott GG 14 3·0 mm. filter. A Zeiss Luminar 1:4.5 lens with a focal length of 63 mm. was fitted to the extension ring and used at full aperture. This combination gives an enlargement of × 1·5.

Focusing is achieved by changing the object distance and viewing the image on a Nikon plan mat focusing screen type D, specially designed for macrophotography.

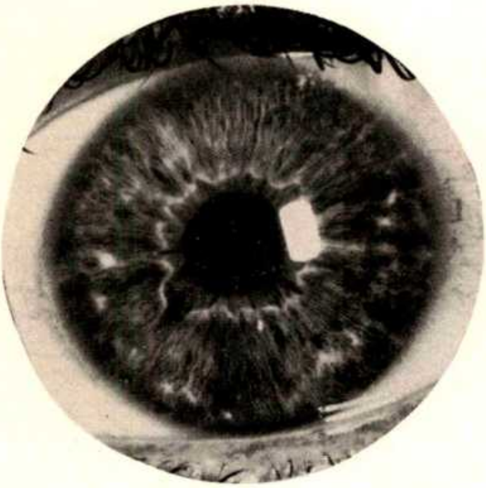
The film, Ilford FP3 (125 ASA) was developed in Promicrol diluted 1:2. The flash unit was set at 740 watt/sec., which gives a flash frequency of 1–2 flashes per second.

The fundus camera is used only to supply the blue excitation light, and the Nickon camera is used to photograph the iris fluorescence.

Results

The description of the results in two patients will suffice as examples of this technique.

Case 1, a 30-year-old man, was used as a normal control subject to demonstrate a normal iris fluorescence angiogram: the iris seemed normal and the iris colour was light blue (Fig. 2). 10 sec. after an intravenous injection of fluorescein 10 per cent., several arteries coming from the annulus major were seen to fluoresce (Fig. 3).



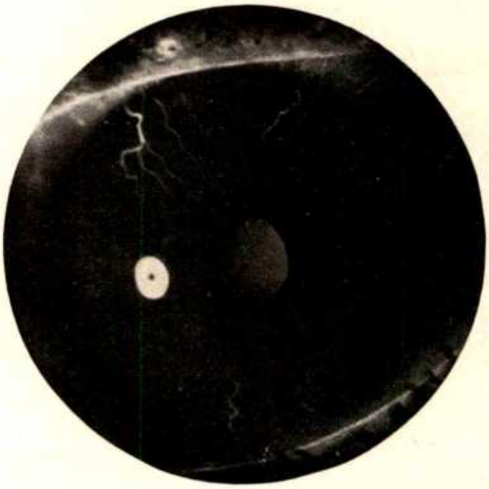


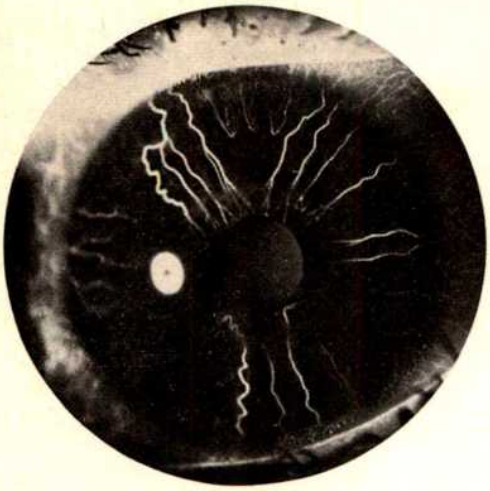
FIG. 2 *Case 1. Black and white photograph of a normal iris.*

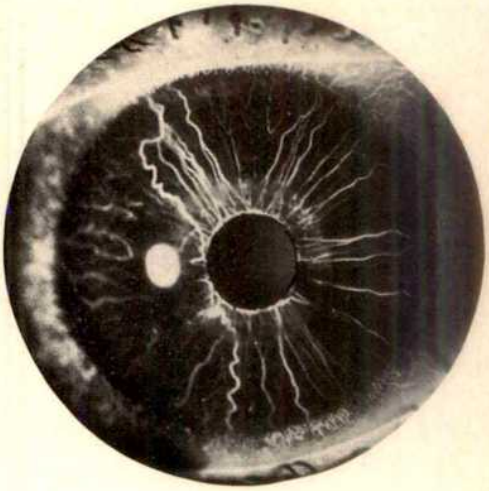
FIG. 3 *Fluorescence photograph: 10 sec., arterial phase: arteries from annulus major fluorescing.*

After 13 sec. the pupillary border was reached, where several collateral vessels were seen to fluoresce (Fig. 4). After 20 sec. a capillary network was fluorescing along the annulus major (Fig. 5). The annulus minor and the pupillary border were seen as a light border in the later phases (Fig. 6).

Case 2, a 45-year-old man, was admitted to the Eye Hospital with a large pigmented iris tumour, over which vessels were seen to course (Fig. 7, overleaf). Fluorescence angiography showed filling of some tortuous vessels within the tumour in the arterial phase 11 sec. after the injection (Fig. 8). In the venous phase after 20 sec. this fluorescence intensified and some very large vessels were seen to fill; some of these vessels even seemed to be thrombosed (Fig. 9). The later pictures showed a diffuse fluorescence with a leakage of fluorescein within the tumour (Fig. 10, overleaf).

At the site of the tumour it would seem that the conjunctival fluorescence is more intense





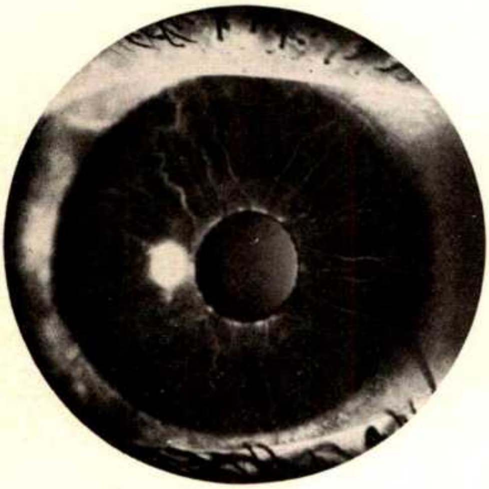


FIG. 4 *Fluorescence photograph:* 13 *sec., the pupillary border is reached where collateral vessels are seen to fluoresce.*

FIG. 5 *Fluorescence photograph:* 20 *sec., fluorescence of capillary network along annulus major.*

FIG. 6 *Fluorescence photograph:* 78 *sec., annulus minor and pupillary border are seen to fluoresce as a light border.*

than outside the tumour area. An examination of the histology of this tumour showed it to be a naevus iridis (Manschot).

Discussion

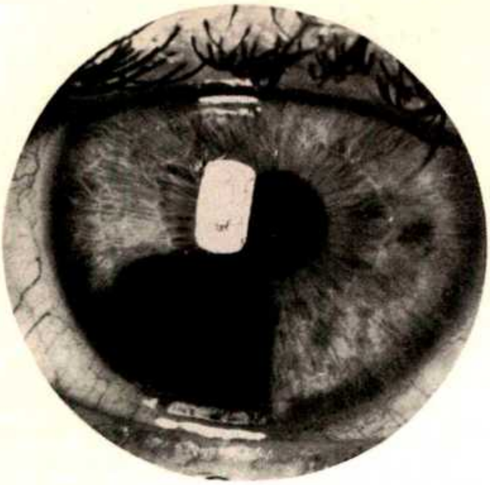
The advantages of this technique are twofold, provided that the photographic department is equipped with a fundus camera that has been modified for fluorescence angiography.

(**1**) No photo slit lamp is needed.

(**2**) The luminar lens is designed to photograph a flat surface, unlike the fundus camera which is specially corrected for a hollow plane such as the fundus, so that photography of a convex structure such as the outer eye results in distortion which is further augmented by the use of a 20 cm. lens in front of the objective.

Furthermore, in the technique described, high-speed film is not necessary, and the film used does not have to be force developed; this means that the enlargements show very little graining.

Last, but not least, the attachment of the motorized Nikon camera, including the extension ring set and the Luminar lens, is much less expensive than an extra flash unit and photo slit lamp.



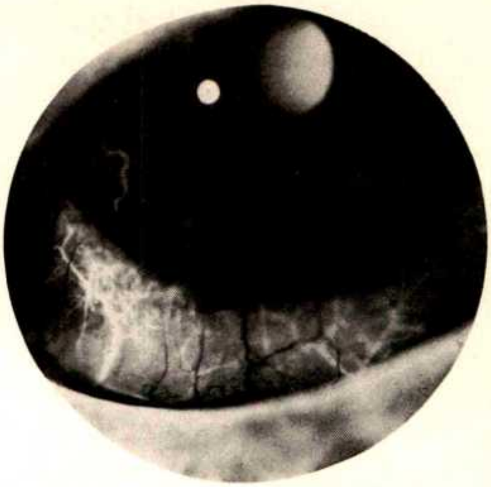
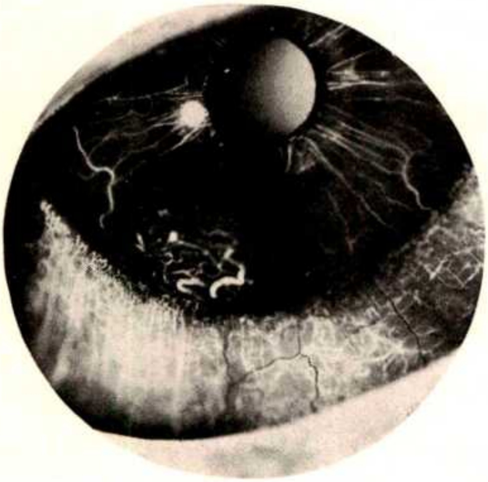


FIG. 7 *Case 2. Black and white photograph, showing a large pigmented iris tumour with vessels coursing over it.*
FIG. 8 *Fluorescence photograph: 10 sec., arterial phase: filling of some tortuous vessels within the tumour.*



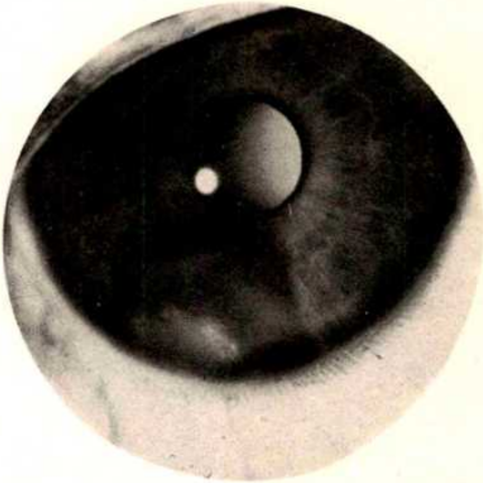


FIG. 9 *Fluorescence photograph: 20 sec., venous phase: fluorescence intensifies, some large vessels are seen to fluoresce.*
FIG. 10 *Fluorescence photograph: 74 sec. : diffuse fluorescence with leakage of fluorescein within the tumour.*

Summary

An iris fluoro-angiographic technique is described, using a Zeiss fundus camera to supply the blue excitation light. The fluorescence is photographed on an external motorized Nikon camera.

A fluoro-angiogram from a normal subject is compared with one from a patient with a naevus iridis.

We are much indebted to Dr. W. A. Manschot for the histological report on the naevus iridis and to Mr. J. J. Roosenmaalen for making the attachments holding the Nikon camera to the fundus camera.

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Serum immunoglobulins in retinal vasculitis

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Perivasculitis is a common pathological reaction in the retina, the veins being affected more frequently than the arteries. It is not a specific disease entity and the majority of cases are thought to result from an allergic reaction to one of a wide variety of antigens (Ashton, 1962). Reviews of the subject have been published by Donders (1958), Goddé-Jolly (1961), Doden (1963), Koliopoulos (1967), Duke-Elder and Dobree (1967), and Charamis (1968).

Clinical and experimental observations strongly suggest that allergic mechanisms play a predominant role in retinal vasculitis (Uyama, 1936; Meyer, 1940; De Muro and Focosi, 1951; Elliot, 1954; Miescher, Paronetto, Borel, and Miescher, 1968). Treatment with immunosuppressives (cortisone, etc.) gives good results, as shown by Elliot (1962) and Cross (1965). Retinal vasculitis can be associated with other ocular or systemic diseases in which immune reactions are probably involved, such as uveitis, Behçet's disease, sarcoidosis, multiple sclerosis, etc., or with infective conditions, such as tuberculosis and brucellosis.

From a clinical and aetiological point of view, retinal vasculitis can be divided into three distinct types:

(a) Secondary to uveitis;

(b) Secondary to systemic disease;

(c) A primary type the aetiology of which is largely conjectural since in most cases no specific cause can be found (Duke-Elder and Dobree, 1967).

This preliminary study was undertaken in an attempt to discover whether there is any correlation between the clinical picture of retinal vasculitis and the humoral components of the immune system.

Material and methods

The serum immunoglobulins of thirteen patients with retinal vasculitis were estimated, using the single radial immunodiffusion plate method as described by Mancini, Carbonara, and Heremans (1965). The normal levels of serum globulins in the control group of healthy adults, obtained by the same method in the same laboratory, were:

For γG* (or IgG) 700 to 1,500 mg./100 ml. serum;
For γA (or IgA) 150 to 450 mg./100 ml. serum;
For γM (or IgM) 50 to 150 mg./100 ml. serum.

Table I shows a comparison of these levels with the mean values obtained by other workers using similar techniques.

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Table I *Mean values of immunoglobulins (mg./100 ml. serum) as assayed by simple radial immunodiffusion*

Authors	*Date*	*Immunoglobulins*		
		γG	γA	γM
Mancini and others	1965	1,200	243	146
McKelvey and Fahey	1965	1,240	280	116
Stiehm and Fudenberg	1966	1,158 ± 305 (569–1,919)	200 ± 61 (61–330)	99 ± 27 (47–147)
Aiuti, Turbessi, Cirelli, de Bac, Martinelli, and Ricci	1967	1,160	177	97
Zanussi and Medina	1967	1,172 ± 190	245 ± 190	105 ± 11
Johnson and Bloch	1969	1,180 ± 310	218 ± 96	98 ± 41
Our normal limits		700–1,500	150–450	50–150

The patients had been followed up for 6 months or more, but investigations had not confirmed any specific aetiology. Those in whom a specific diagnosis was established, *e.g.* toxoplasmosis, rheumatoid arthritis, or other systemic disease, were excluded. The series included cases of primary retinal vasculitis and vasculitis secondary to an active or an old uveitis. The cases of primary vasculitis were divided into two types:

(a) Peripheral, more closely resembling the classical picture of Eales's disease;

(b) Central, of the type described by Lyle and Wybar (1961).

Some of the patients with the central type had been diagnosed initially as having a central vein thrombosis, but the rather low age range (27 to 47 years), the retention of good vision, and the ophthalmoscopic picture suggested a central type of vasculitis.

Results

The concentrations of the three major immunoglobulins (γG, γA, γM) determined by the radial immunodiffusion method in the thirteen patients are shown in Table II (opposite).

The immunoglobulin levels in those with the central type of vasculitis were within normal limits, except in Case 4 in whom the γM was raised. In cases of peripheral vasculitis, the γM levels were near the lower limit of normal, and Case 7 had a very low value (25 mg./100 ml. serum). By contrast, all four with vasculitis secondary to uveitis had serum concentrations of γM above the limit of normal.

Discussion

The responses of the immune system can be broadly divided into two groups, humoral and cellular. The humoral antibody responses are based on antibody molecules, the immunoglobulins γG, γA, γM, γD, γE (in decreasing order of concentration). These are synthesized by immunologically activated cells. The cellular immune responses are carried out by sensitized cells, mainly lymphocytes. Estimation of the serum levels of immunoglobulins indicates the degree of the patient's immunological response as far as humoral antibodies are concerned.

If retinal vasculitis is the result of an allergic reaction, some alteration of circulating antibodies might be expected in patients with this condition. Johnson and Bloch (1969) reported a series of four patients with Eales's disease in whom the mean level of γG was

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* The terminology is that suggested by the World Health Organization Nomenclature Committee (*Bull. Wld Hlth Org.*, **30**, 447, 1964).

Symbols proposed	*Previous usage*
γG or IgG	γ, 7Sγ, 6·6Sγ, γ_2, γ_{ss}
γA or IgA	β_2A, γ_1A
γM or IgM	γ_1M, β_2M, 19Sγ, γ-macroglobulin

Table II *Serum immunoglobulin concentrations (mg./100 ml.) in patients with retinal vasculitis*

Type of vasculitis	*Case no.*	*Sex*	*Age (yrs)*	*Immunoglobulins* γG	γA	γM
Central	1	F	47	1,150	350	75
	2	M	38	1,050	425	130
	3	M	27	1,000	380	82
	4	F	32	1,050	187	165
Means				1,062	336	118
Peripheral (Eales's disease)	5	M	31	1,000	150	67
	6	M	24	1,200	210	70
	7	F	62	720	230	25
	8	M	40	1,300	390	62
	9	M	34	880	380	80
Means				1,020	252	61
Secondary to uveitis	10	F	39	1,000	80	400
	11	M	32	920	310	160
	12	M	30	1,100	225	160
	13	F	23	1,300	175	155
Means				1,080	198	219
Controls				700–1,500	150–450	50–150

raised (1,512 mg./100 ml. ±259) but in whom the γM levels were within normal limits (70-145 mg./100 ml.). In our series the γG immunoglobulins were not increased in Eales's disease, but the mean level of the γM immunoglobulins was low, and one patient had only 25 mg./100 ml. serum.

The most striking finding in our series concerned patients in whom the vasculitis was considered to be secondary to uveitis. All four had raised levels of γM immunoglobulin. Raised γM levels have been reported in uveitis by Aronson (1968), but as an elevation of γM occurs in many virus infections it is difficult to postulate any specific relation between uveitis and abnormal immunoglobulins on the basis of the present evidence. One of our patients with uveitis had a low serum γA level, but the significance of this finding is not known.

Uveitis is often associated with connective tissue disorders (Duke-Elder and Perkins, 1966), but there was no evidence of such an association in this series. It may be that the high levels of γM represent an increase in antibody to an unrecognized micro-organism or other antigen. On the other hand it is possible, as Aronson (1968) suggested, that individuals with high levels of γM are more susceptible to uveitis. Our results and those of other workers suggest that further investigation of the immunological responsiveness of patients with uveitis and retinal vasculitis would be worthwhile.

Summary

In thirteen cases of retinal vasculitis the serum immunoglobulins were determined by the single radial immunodiffusion method. An elevation of γM was found in four cases secondary to uveitis. In the central type of retinal vasculitis the levels of the three major

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immunoglobulins (γG, γA, γM) were within normal limits, but in cases of the peripheral type (Eales's disease) a low level of γM was found. The significance of these results is discussed.

We should like to thank Prof. I. D. P. Wootton and Dr. J. R. Hobbs, of the Department of Chemical Pathology, Royal Postgraduate Medical School, where the immunoglobulin estimations were carried out, and the Surgeons of Moorfields Eye Hospital for their help in referring cases.

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Ocular complications after therapeutic irradiation

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At one time radiotherapy had a sinister reputation amongst ophthalmologists because of the frequent and often disastrous sequelae of ocular irradiation; cataract was common, the eyelids and the eye-ball sometimes underwent necrosis, and very occasionally malignant changes developed in irradiated tissues. Over the years increasing knowledge of the effects of radiation, refinements in techniques and dosage, and the development of protective devices associated with increasing liaison between eye surgeons, radiotherapists, and physicists have established the place of radiation in the treatment of eye disease.

Radiotherapy now has an accepted and increasingly important place in the treatment of intraocular tumours, particularly retinoblastoma, malignant melanoma of the choroid, and secondary deposits from primary tumours elsewhere in the body (Bedford, 1968) rhabdomyosarcoma of the orbit (Sagerman, Cassady, and Tretter, 1968), and also external ocular neoplasms such as basal and squamous-cell carcinoma of the eyelids and certain melanotic lesions (Lederman, 1958). Apart from these malignant conditions, several non-malignant diseases have been treated in the past, but at present radiotherapy is being used in only a few, such as certain cases of vernal catarrh and rosacea keratitis (Lederman, 1957), pterygium (Hilgers, 1966), and corneal vascularization following keratoplasty (Leigh, 1966).

Complications may arise with all forms of radiotherapy but vary with the different ocular tissues involved and the form of radiation used. Some of these effects are transient and insignificant; others are permanent and may or may not impair the structure or function of the eye. This account is based on a study of side-effects observed in cases of eyelid and ocular tumours treated in the Tumour Unit of Moorfields and St. Bartholomew's Hospital, London.

Clinically, the complications which may arise in some patients after therapeutic irradiation of the eye and adjacent structures may be divided into two groups:

(**1**) *Acute* Those of early or rapid onset are usually reversible;

(**2**) *Chronic* Those of delayed onset are usually irreversible.

The present study is mainly concerned with these delayed effects, and it is convenient to consider this problem on an anatomical basis.

EPILATION

Loss of eyelashes frequently follows the treatment of rodent ulcers of the eyelids with *x* rays; in most cases this is likely to be permanent but apart from cosmetic considerations

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is of no consequence (Fig. 1). Epilation of scalp hair is common at the exit portal after cobalt beam therapy using a direct anterior field for the treatment of retinoblastoma (Skeggs and Williams, 1966), but usually the hair grows again (Fig. 2). Loss of eyebrow hair (Fig. 3) may result from the application of a cobalt plaque for treatment of a malignant melanoma of the choroid, but this complication is extremely rare and is usually accompanied by evidence of damage to the lacrimal gland which will be discussed later.

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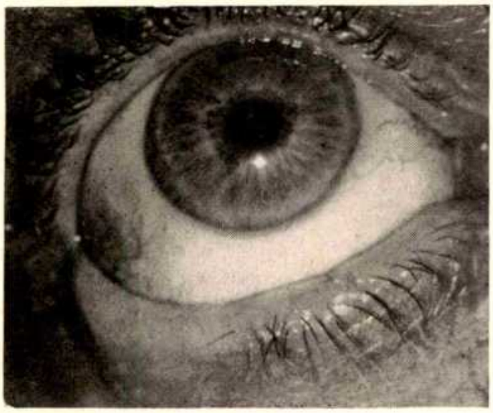

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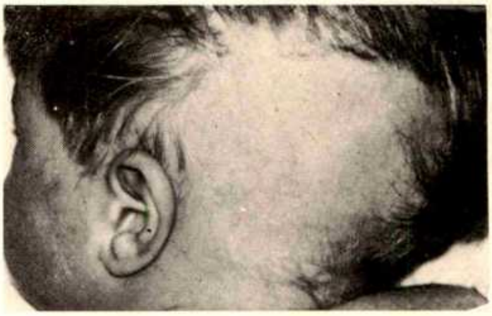

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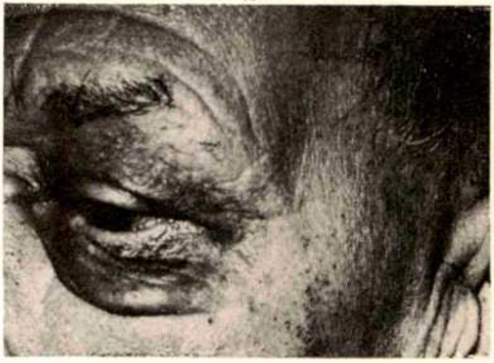


FIG. 1 *Localized loss of eyelashes after radiotherapy for basal cell carcinoma of eyelid*

FIG. 2 *Epilation after cobalt beam therapy using an anterior field*

FIG. 3 *Loss of the outer half of the eyebrow due to application of a cobalt plaque for a malignant melanoma of the choroid*

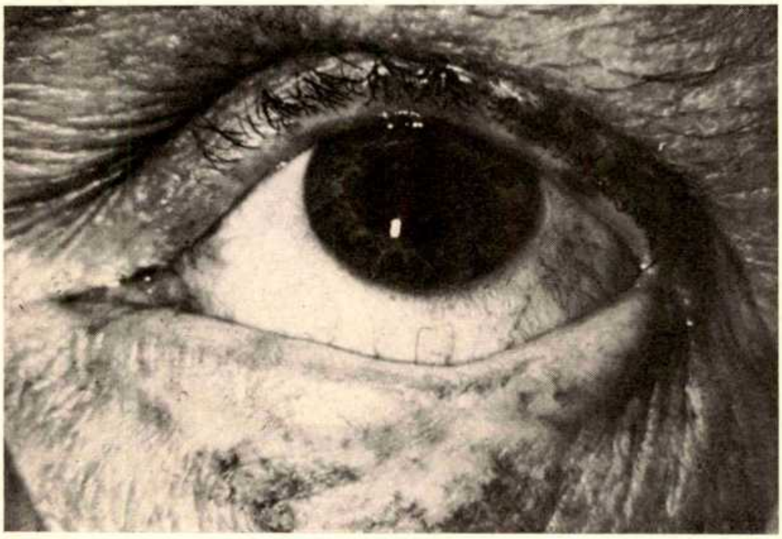


FIG. 4 *Skin changes after irradiation for basal cell carcinoma of the eyelid, showing epilation, depigmentation, telangiectasia, and atrophy*

SKIN

Most palpebral tumours treated by radiation show the well-known acute radiation erythematous reaction which generally settles within a few weeks. At a later stage permanent changes may appear, such as depigmentation, atrophy, and telangiectasia, but these effects are usually relatively minor and harmless (Fig. 4). Shrinkage of the tissue of the lid is rare with modern techniques, but ectropion and entropion may develop in this way. In the past occasional cases of postradiation cancer developing in the periocular tissues have been reported (Cade, 1957; Forrest, 1962), but no such cases have occurred in our experience nor have we seen radiation necrosis of the eyelids.

CONJUNCTIVA

In the treatment of a cutaneous basal or squamous cell carcinoma with *x* rays, the whole thickness of the lid receives a tumour-lethal dose, which may, in addition to the dermal changes previously mentioned, be followed by changes in the palpebral conjunctiva. These may take two forms:

(1) *Telangiectasia*, which is of no significance (Fig. 5);

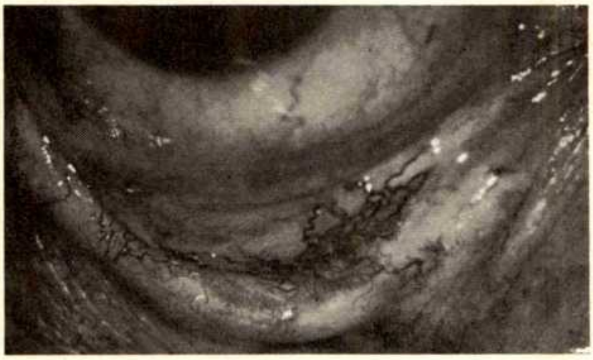


FIG. 5 *Localized telangiectasia of the palpebral conjunctiva*

(2) *Formation of keratin plaques* (Fig. 6), which, particularly if in the centre of the upper eyelid, may cause abrasion of the cornea with discomfort (Lederman, 1957; Bedford, 1966).

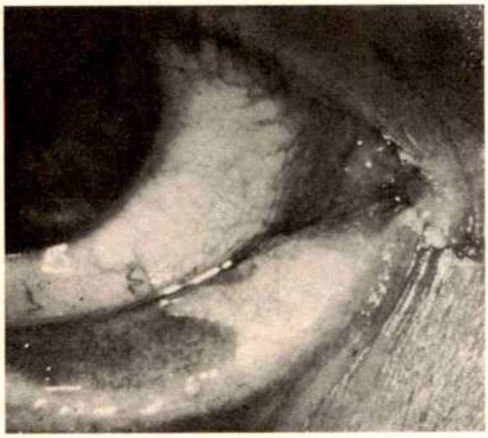


FIG. 6 *Keratin plaque*

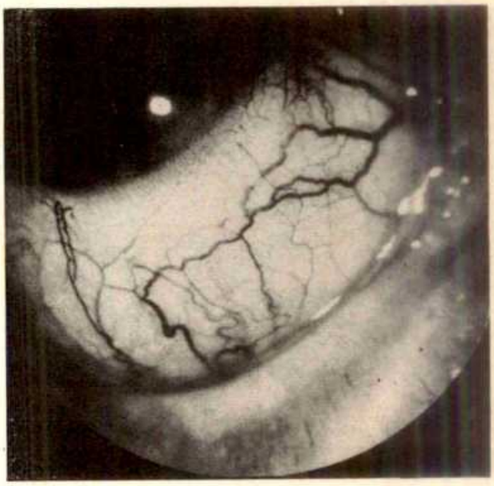


FIG. 7 *Extensive telangiectasia involving the whole of the bulbar conjunctiva and associated with secondary open-angle glaucoma*

Similar telangiectasia can develop in the bulbar conjunctiva and if generalized (Fig. 7) may be associated with secondary open-angle glaucoma (Bedford, 1966). Localized telangiectasia has also followed the application of an anteriorly placed cobalt plaque but apparently without any harmful effect. These vascular changes have also been seen after the use of beta-radiation for localised conjunctival lesions, but not when such treatment has been applied for corneal disease. The additional effects on the conjunctiva when lacrimal secretion is defective will be discussed later. As a very rare complication, because of the enormous dose of radiation emanating from the back of an anteriorly-placed cobalt plaque, conjunctival necrosis has been followed by the formation of symblepharon.

CORNEA

Apart from the temporary punctate epithelial erosions seen commonly as an acute radiation reaction, delayed corneal complications may arise either as a direct result of radiation on the corneal tissues or as a complication of the "dry-eye" syndrome due to reduced or absent lacrimal secretion. Corneal necrosis has been described as an early result of high doses of radiation, but this is very rare and is more likely to appear some months after the completion of treatment (Blodi, 1958; Linnell and Wolter, 1967). Decrease of corneal sensitivity to the point of complete anaesthesia is a typical early sign of radiation keratopathy; the concomitant absence of ocular pain may give rise to a false sense of security and delay the recognition of corneal ulceration. Such ulceration is characteristically indolent involving the greater thickness of the cornea and may be central or marginal and in the latter case either localized or circumferential in extent (Fig. 8). Eventually healing may take place with much neovascularization and scarring of the cornea, or rarely the tissue destruction may progress insidiously to complete necrosis with perforation of the eye and possibly with extrusion of the intraocular contents. These serious complications are likely to occur only after high dosages with *x* rays but have also been seen with beta-radiation. A rare type of corneal dystrophy has also been seen after beta-radiation, characterized by epithelial and stromal oedema (Fig. 9) with loss of corneal sensation but without any rise of the intraocular pressure. Such changes are probably due to interference with the integrity of Descemet's membrane (Bedford 1966).

(8)

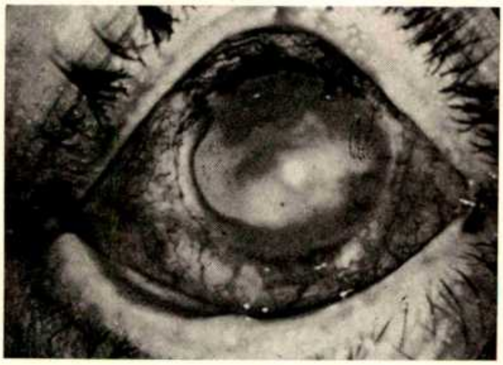


FIG. 8 *Severe keratopathy after β-irradiation for conjunctival cancerous melanosis. There is an indolent peripheral gutter-like ulcer on the nasal side and extensive opacification of the corneal stroma*

(9)

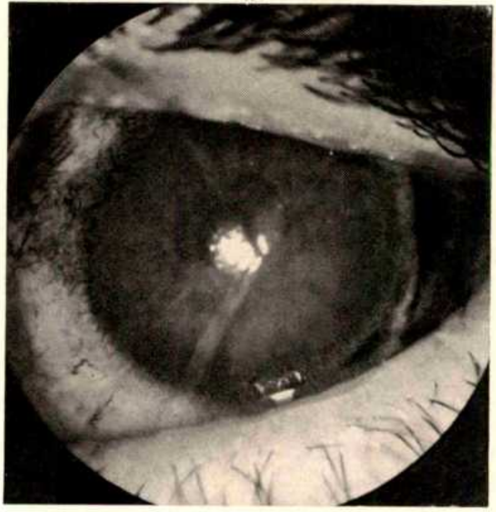


FIG. 9 *Earlier stage of condition seen in Fig. 8, showing epithelial and stromal oedema*

Finally, radiation damage to the lacrimal gland may result in decreased or absent lacrimal secretion with consequent drying of the surface of the eye; when this happens the cornea loses its characteristic clarity, the surface becomes rough and shows staining points with Bengal rose, and filaments can be seen on the surface of the cornea and conjunctiva, these changes giving rise to considerable ocular discomfort (Fig. 10).

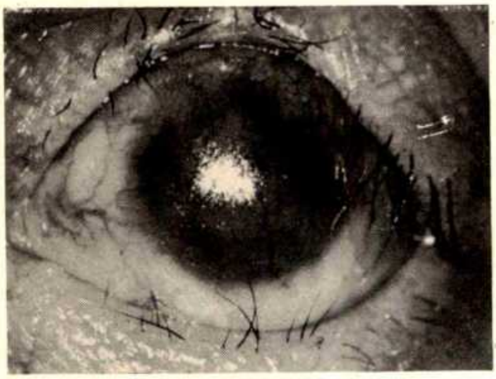


FIG. 10 *Extreme example of radiation keratopathy associated with diminished lacrimal secretion after cobalt beam therapy (using a direct anterior field) for a malignant melanoma in an only eye when all other conservative therapy had failed. Histological examination of the enucleated eye showed that the tumour had satisfactorily regressed but such heroic therapy is clearly of little clinical value*

SCLERA

Complications after irradiation rarely affect the sclera because this avascular tissue is remarkably radioresistant. Scleral necrosis occasionally followed the use of radon seeds or tantalum wire implants. We have, however, seen such a condition in a woman treated for a choroidal melanoma with a large cobalt plaque (15 mm.) applied on two occasions leading to a very high dose of radiation to the sclera (approximately 80,000 r. (Fig. 11)). The eye was subsequently removed. Scleral necrosis has also been described after beta-radiation for a localized lesion near the limbus, again after very high dosage in the region of at least 10,000 r (Jones and Reese, 1953).

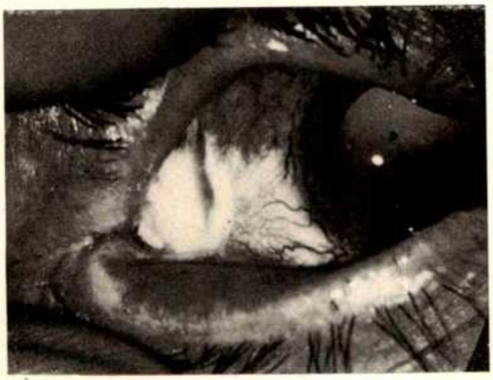


FIG. 11 *Scleral necrosis adjacent to lateral canthus after application of a large cobalt plaque on two occasions for a malignant melanoma in an only eye*

ANTERIOR CHAMBER

Complications are rare except after high dosages of radiation for intraocular tumours. Thus, if a cobalt plaque is applied after irradiation of the whole eye with cobalt beam therapy for retinoblastoma, iridocyclitis may lead to extensive posterior synechiae (Fig. 12, overleaf); rubeosis of the iris has been seen and may cause bleeding into the anterior chamber; a rare and harmless side-effect is a peculiar form of sectoral iris atrophy (Fig. 13, overleaf), probably due to localized ischaemia resulting from the application of a cobalt plaque close to the iris root.

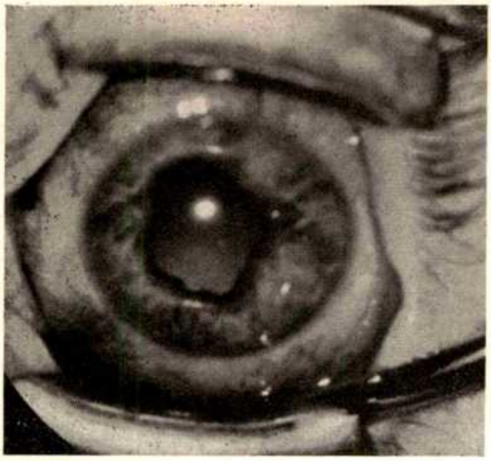


FIG. 12 *Extensive posterior synechiae after repeated irradiation for recurrent retinoblastoma*

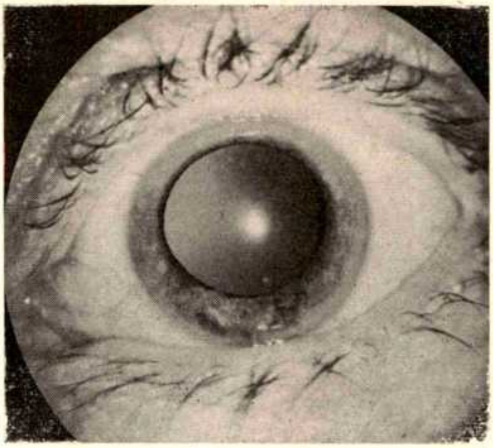


FIG. 13 *Localized iris atrophy extending from 5 to 8 o'clock after treatment of a peripheral choroidal malignant melanoma in this sector. A marked degree of pigmentary iridopathy was apparent on retro-illumination*

LENS

Opacification of the lens is the classical change described in eyes subjected to therapeutic radiation. However, such opacities—which must be distinguished from pre-existing senile or congenital lens opacities—are not always complete, and if they progress at all may do so only very slowly. Lens opacities can be expected to occur after high voltage therapy, 500 to 1,000 r being cataractogenic, but cataract has resulted from a single dose of as little as 200 r (Merriam and Focht, 1957), and with certain forms of treatment their times of appearance can be forecast with considerable accuracy. Four main types of cataract may be seen:

(1) *The doughnut cataract* This is the classical type following exposure to radiation from nuclear explosions, and in our experience usually occurs about 2 years after cobalt beam therapy for retinoblastoma delivering over 4,000 r with the direct anterior field (Fig. 14). In those cases where gross visual loss results from the opacity, surgical treatment gives good results.

(2) *Posterior sub-capsular cataract* In this type the whole posterior part of the lens becomes opacified, resulting in considerable reduction in visual acuity. This change can also occur after the use of cobalt beam therapy (Fig. 15).

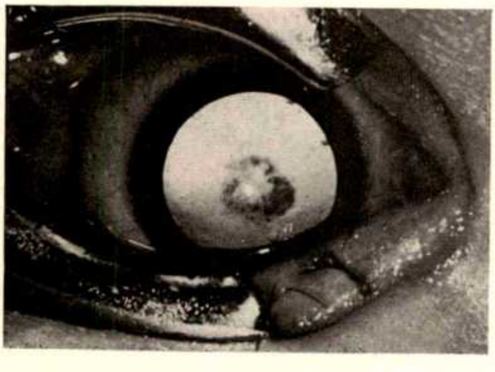


FIG. 14 *Classical doughnut radiation cataract*

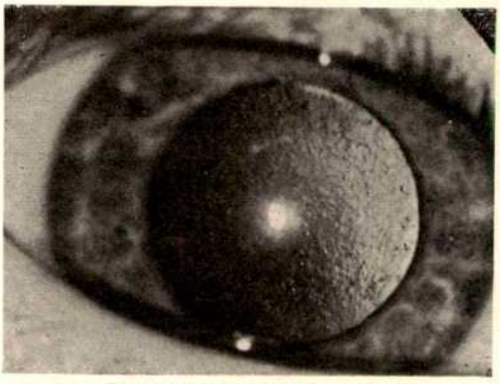


FIG. 15 *Posterior sub-capsular lens opacity*

(3) *Sectoral lens opacities* These occur occasionally when a cobalt plaque has been placed near the ora serrata and therefore close to the equator of the lens where the germinative epithelium is situated (Fig. 16). Similar localized nonprogressive lens opacities may also be seen after beta-radiation for a lesion at the limbus. Both these types of localized lens opacity are hidden behind the iris and do not impair vision; thus they will not be found unless the pupil is dilated. According to Hilgers (1966) these localized lens changes are unlikely to appear with a fractionated total dose of under 5,000 r and they do not as a rule progress to complete opacification unless subsequent radiation boosts the total dose received by the lens.

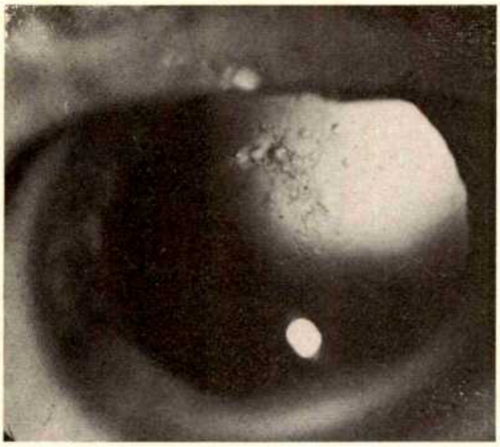
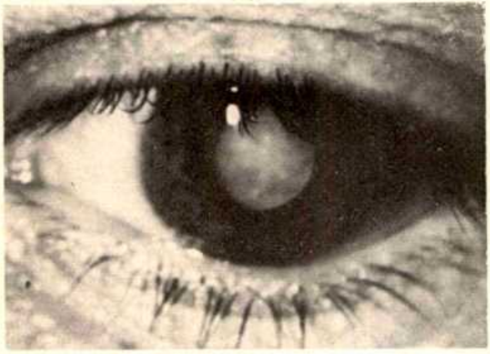


FIG. 16 *Localized lens opacity (which is apparently non-progressive and does not interfere with vision) following the application of a cobalt plaque*

(4) *Complete total cataract* Complete opacification of the lens is rare but may follow about 2 to 3 years after irradiation of the whole eye; for example, in the treatment of paranasal sinus disease (Fig. 17), or when radiation has been given to an eye in which secondary retinal detachment is present, as for instance with a retinoblastoma (Fig. 18).

(17)



(18)

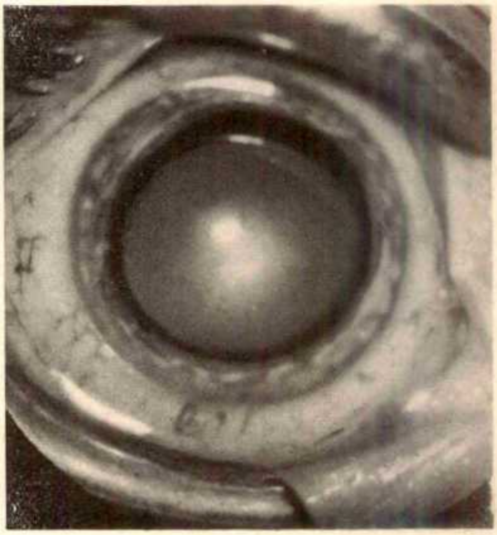


FIG. 17 *Total cataract 2 years after irradiation for carcinoma of the sphenoid sinus*

FIG. 18 *Total opacification of the lens associated with an extensive retinal detachment secondary to a retinoblastoma treated with the cobalt beam*

RETINA, CHOROID, AND OPTIC DISC

In our experience radiation retinopathy rarely occurs after irradiation of the whole eye and such changes are uncommon unless doses in the region of 6,000 r or more are used (Chee, 1968). Retinal and choroidal changes, however, are commonly seen after local irradiation for retinoblastoma and choroidal malignant melanoma when these tissues receive doses ranging between 20,000 and 40,000 r. Increasing awareness of these side-effects, which may not be apparent until some months after the completion of treatment, has helped to define more closely the indications for the use of cobalt plaques in the treatment of intraocular tumours.

The effects on the choroid, retina, and optic disc may be as follows:

(1) *Vascular changes* Narrowing and obliteration of the retinal arteries, veins, and capillaries is frequently found up to a year after the use of a cobalt plaque for a malignant melanoma. In cases in which massive radiation to the retinal vessels has necessarily been incurred, the vessels may show perivascular white sheathing and may later even become completely occluded, appearing as solid white cords. The resulting ischaemia of the retinal neuro-epithelium leads to progressive visual loss and optic nerve atrophy which may be complete if a cobalt plaque has been placed within a few millimetres of the optic disc. In several of our cases destruction of the tumour in this way has been followed by complete loss of sight in the affected eye 15 to 18 months after treatment (Fig. 19).

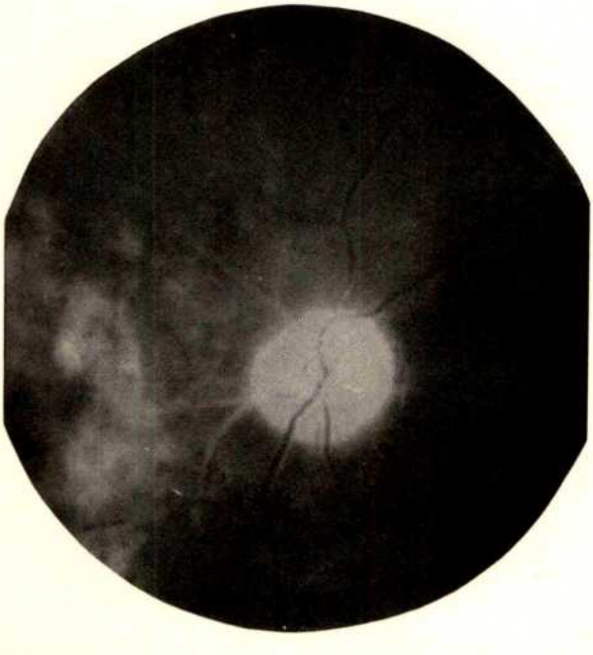


FIG. 19 *Gross optic atrophy and complete obliteration of central retinal artery after successful application of a cobalt plaque to a juxtapapillary malignant melanoma, the debris of which can be seen on the left. The eye was blind*

(2) *Appearance of exudates* Haemorrhages in and around the treated area appear at an early stage and are not uncommonly seen about 12 months after focal irradiation with a cobalt plaque for a juxtapapillary retinoblastoma. Such haemorrhages, which are rarely seen with peripheral tumours, may break into the vitreous causing a decrease in vision, but as a rule spontaneous clearing takes place. With a peripheral tumour also telangiectasia often develops, but does not usually give rise to intraocular haemorrhage. Exudates are generally hard and white presumably the result of phagocytosis of tumour debris or

haemorrhage together with infarction of choroid and retinal tissue close to the tumour. They may also appear at the macula in the form of a star pattern or as a circinate retinopathy (Fig. 20). These exudates persist and may cause a serious decrease in vision, even when the tumour is situated some distance from the posterior pole. Soft white exudates or cotton-wool spots may be seen at an early stage after treatment but rapidly disappear.

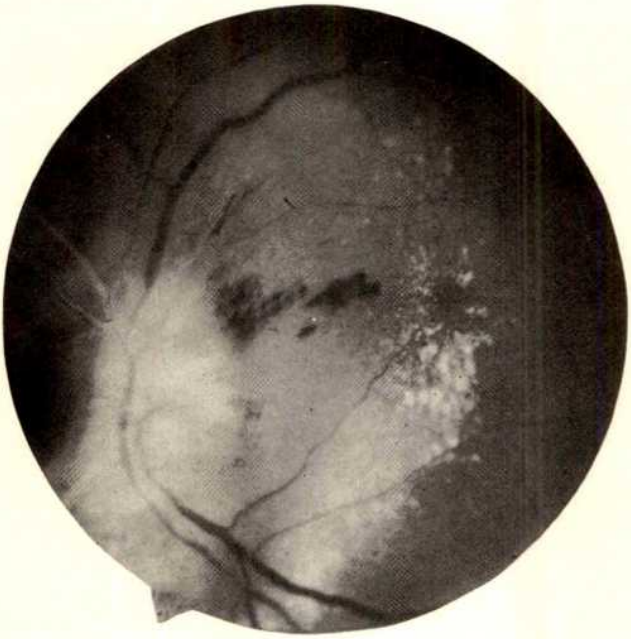


FIG. 20 *Radiation retinopathy: haemorrhages, exudates, and arterial occlusion after application of a C-shaped cobalt plaque*

(3) *Disturbance of the pigment epithelium* The pigment epithelium reacts in two ways—first, by migration of pigment giving discrete fine stippling in the area around the base of the tumour (Fig. 21), and secondly, by a more generalized pigment dispersal if whole-eye irradiation has been used. The latter change may be more related to repositioning of a pre-existing long-standing retinal detachment rather than to irradiation. Changes in the choroidal vessels progress from telangiectasia through varying degrees of obliteration to complete disappearance and this sequence combined with retinal vessel and pigmentary

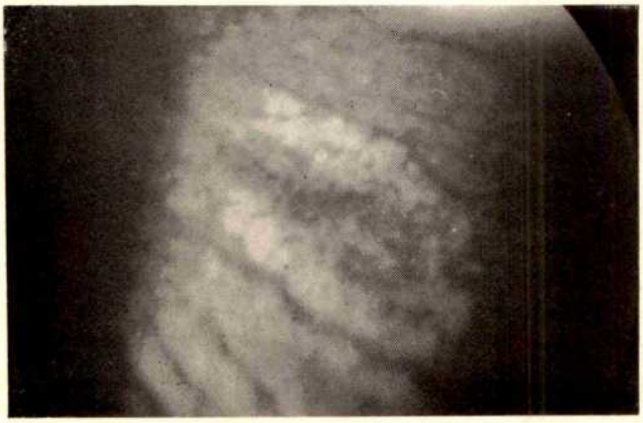


FIG. 21 *Pigmentary changes after application of a cobalt plaque. The edge of the melanoma is seen on the left; normal retina and choroid are seen on the right; there is patchy depigmentation and attenuation of the choroidal vessels in the centre*

changes may give rise to the appearance of massive choroido-retinal atrophy, leaving bare sclera exposed, as used to be seen commonly with radon seeds.

Because of the vascular changes in the choroid and retina already mentioned and the associated retinal neuro-epithelial degeneration, atrophy of the optic nerve is inevitable when a massive dose of radiation is applied adjacent to the optic disc. These irreversible changes and the consequent dramatic loss of vision have led us to discontinue the use of the C-shaped cobalt plaque.

GLAUCOMA

Secondary glaucoma may occur when generalized telangiectasia of the conjunctival vessels has followed irradiation of the anterior segment (Bedford, 1966), or it may be associated with rubeosis of the iris and anterior chamber angle (Jones, 1958), or occasionally it may result from haemolytic changes associated with intraocular haemorrhage causing obstruction of the outflow channels. Whereas, in the first condition, a drainage operation may help to control the ocular hypertension, in the other two conditions the eye is seriously damaged and no treatment is likely to be permanently successful.

LACRIMAL GLAND

Radiation damage to the lacrimal gland and its ducts may follow the use of a cobalt plaque placed anteriorly to the equator on the temporal side of the globe because of the tremendous amount of radiation emanating from the edge and posterior surface of the plaque. It may also follow the use of conventional *x* rays or radon seeds for the treatment of neoplasms of the outer canthus. Decreased or absent tear secretion results in a "dry-eye" syndrome with symptoms of irritation and discomfort; rose Bengal staining of the conjunctiva and cornea can be seen together with epithelial filaments.

LACRIMAL PASSAGES

When radiation is used for the treatment of neoplasms at the inner end of the eyelids and in the region of the lacrimal sac, occlusion of the canaliculus, sac, and naso-lacrimal duct commonly results. However, this does not seem to be a serious problem and watering of the eye does not in fact occur as often as is commonly thought. Syringing of the lacrimal passages is of little value in the prevention or treatment of this complication and in our experience surgical treatment has not been indicated.

ORBIT

Irradiation in a child is likely to interfere with the ossification centres, leading to retardation of growth on the affected side and subsequent asymmetry of the orbits. When radiotherapy follows the removal of an eye, postradiation contracture of the conjunctiva leading to a shrunken socket is less likely to occur if a plastic shell is in place during treatment; however, some degree of contracture of the socket must be expected, especially if radiation has been used before enucleation. Postradiation malignant change in bone has been described (Forrest, 1962; Soloway, 1966; Sagerman, Cassady, Tretter, and Ellesworth, 1969), but we have not seen any cases of bone sarcoma in the past 5 years. It is, however, possible that such malignant change may develop in the future as a result of the high dosage from a cobalt plaque placed under the medial rectus muscle close to the ethmoid bone.

Summary

Radiotherapy has a valuable place in the treatment of neoplastic disease of the eye and orbit.

Conventional *x* rays and modern radiotherapeutic techniques may lead to complications, the majority of which are of relatively minor importance.

Cobalt plaques are being increasingly used in centres throughout the world and are proving of considerable value for otherwise incurable conditions. Increasing awareness of their side-effects, particularly on the optic nerve, should lead to careful consideration not only of the size but also of the site of the neoplasm, bearing in mind the very high radiation dose inevitable with this technique.

Further work is being done to define more closely the indications for the application of cobalt plaques in the area of the optic disc and to elucidate the pathology of the vascular changes in radiation retinopathy.

We should like to thank the Medical Illustration Department at the Institute of Ophthalmology, London, for help with the illustrations and Miss Heather Payne for secretarial assistance.

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An unusual case of homocystinuria

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Homocystinuria, an inborn error of amino acid metabolism, was discovered independently by Carson and Neill (1962) and Gerritsen, Vaughn, and Waisman (1962). The ocular manifestations have been well described by Presley and Sidbury (1967).

A boy aged 8½ years presented with a 2-week history of an irritable bloodshot left eye after being injured by a snowball.

The eye was injected and there was an area of corneal oedema where the lens was in contact with the posterior corneal surface. The lens was dislocated antero-inferiorly and the intraocular pressure appeared to be raised on digital examination. Externally the other eye appeared normal.

The patient was admitted to hospital and treated with topical steroids and Diamox. A mydriatic trial was performed on the right eye to investigate zonular function, and the anterior chamber became appreciably shallow through anterior displacement of the lens. Mydriatics were discontinued and miotics were substituted; these were required for 2 days before the anterior chamber deepened to its pre-test state. The intraocular pressure was at no time raised in this eye.

Following this test, a provisional diagnosis of homocystinuria or Marfan's syndrome was made. Examination of the urine (R.J.P.) revealed a strongly positive cyanide nitroprusside test. Amino-acid chromatography and electrophoresis confirmed the presence of homocystine in the urine.

General examination (R.R.G.)

The patient was a pleasant mentally-retarded boy, 49" in height and weighing 4 stone (Fig. 1). His hair was brown and there was no malar flush. He had severe genu valgum (Fig. 2), more pronounced on the right side with surgical scars over the inner aspects of the knee joints. There was also pes planus. He had a characteristic "Chaplinesque" gait and walked with his arms in a bowed position because of stiff upper limb joints. There was a *café au lait* spot in the right groin, bilateral femoral bruits, and absent dorsalis pedis pulses. Blood pressure 100/70. Electrocardiogram normal.

Past history and family history

The mother had noted her son's eyes "shimmering" for some years. At 2 years old he had been seen by an orthopaedic surgeon because of late walking. Bilateral genu valgum was thought to be due to late rickets and was treated surgically. At 4 years radiological and biochemical studies were performed because a metabolic defect was suspected. Calcium and phosphorus metabolism was normal. Amino-acid chromatography showed "moderate amounts of glycine and serine, small amounts of histidine and alanine—a normal pattern". At 6 years he was operated on for tongue-tie in view of his defective speech. There was no improvement and his I.Q. was found to be 56. At 8 years he underwent further orthopaedic surgery.

The boy is the third child of unrelated white parents. They and three siblings (one newborn girl, two brothers) have been examined, but there is no biochemical or physical evidence of homocystinuria. One other sibling was postmature and died on the day of birth.

Ocular surgery

In view of the persistent dislocation of the left lens, with corneal contact, and continuing irritability of the eye, it was decided to remove the left lens. 25 g. oral glycerol was given preoperatively and general anaesthesia used. A conventional *ab externo* incision was made. The iris was found to be adherent to the posterior corneal surface above and a broad iridectomy was performed. Cryo-extraction of the lens in capsule was carried out with some vitreous loss. To prevent vascular complications, intravenous heparin 20,000 units was administered at the time of operation and for 3 subsequent days.

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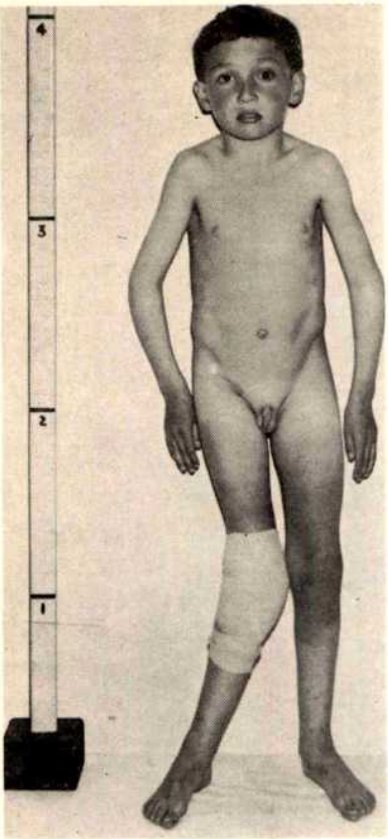

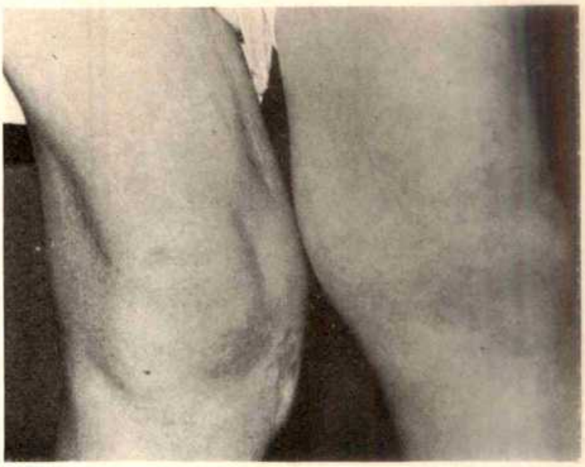

FIG. 2 *Genu valgum*

FIG. 1 *General appearance*

Postoperative recovery was uneventful. The eye remained irritable for about 10 days and was treated with local mydriatic and steroid drops. There was a marked vitreous haze which obscured all fundus details for one month. On subsequent fundus examination, marked left optic atrophy was discovered. The retinal vasculature was attenuated and the peripheral retina thin and atrophic. The left eye is completely blind. The right eye sees 6/18 with −16 D sph., + 4 D cyl., axis 90°.

Gonioscopy

Both angles are open with multiple fine iris processes and marked pigmentation of Schwalbe's line. The angles are abnormal compared with those of the two brothers.

Discussion

The diagnosis of homocystinuria depends on characteristic ocular findings, physical appearance, and biochemical abnormalities.

(a) CHARACTERISTIC OCULAR FINDINGS (Arnott and Greaves, 1964) emphasized the characteristic dislocation of the lens. This is inferior in direction in contradistinction to other disorders such as Marfan's syndrome, Marchesani's syndrome, and congenital ectopia lentis.

The patient in the present report is of interest in that the dislocation was at first considered to be due to external trauma and not to homocystinuria. However, the ease with which dislocation was produced in the contralateral eye raised the possibility of a metabolic defect as the primary lesion. The mydriatic test in the right eye was not entirely free of risk—witness the fact that miotic therapy was required for 2 days before the anterior chamber returned to a normal depth.

Reports of optic atrophy and changes in the retinal vasculature are limited. Presley and Sidbury (1967) described two Negro siblings and one white girl with bilateral optic atrophy. Mukuno, Matsui, and Haraguchi (1967) described one case with retinal angiosclerosis and white sheath formation along the arterioles. Wilson and Ruiz (1969) described a 6-year-old Negro boy who developed bilateral acute glaucoma, and in whom examination under general anaesthesia one month later revealed bilateral central retinal artery occlusions with optic disc pallor.

The optic atrophy and retinal vessel attenuation in the present case are also complicated by the previous history of trauma. In the absence of marked pigmentary scarring at the posterior pole, it may be concluded that the metabolic defect was primarily responsible. In view of the vasculitis affecting the lower limbs, it is possible that the blood vessels to the optic nerve and retina are similarly involved. Furthermore, the secondary glaucoma which was undoubtedly present before operation may have been an additional factor in the development of optic atrophy although the disc was not cupped. Wilson and Ruiz (1969) expressed similar views regarding the aetiology of the optic atrophy.

(b) PHYSICAL APPEARANCE The malar flush, blonde hair, genu valgum, and mental deficiency have been described (Carson, Dent, Field, and Gaull, 1965). If the appearance is atypical, the diagnosis of homocystinuria may not easily be made. Our patient has brown hair and no evidence of malar flush. Furthermore, the genu valgum was noted to be markedly progressive and required multiple orthopaedic procedures; the progressive nature of genu valgum in homocystinuria has not hitherto been described.

40 per cent. of cases of homocystinuria develop fatal thromboses (Carson, 1969) commonly after general anaesthesia. This patient has had general anaesthesia on six occasions, but has shown no sign of thrombosis in spite of lower limb vasculitis.

(c) BIOCHEMICAL ABNORMALITY The urine at the age of 4 years was said to have a normal pattern. It is obvious therefore that homocystine in the urine may not always be detected. The amount excreted may be small (as little as 50 mg. per day) depending on protein intake and possibly on the amount converted to other metabolites.

The presence of homocystine in the urine may be suspected when there is a positive cyanide nitroprusside test. This test is also weakly positive in the presence of raised cystine levels, which commonly occur in heterozygous carriers of certain types of cystinuria. Because of this, low levels of homocystine in the urine giving a weak positive test may be missed or misinterpreted.

The most reliable indication of homocystine in the urine is its demonstration by electrophoresis or chromatography. A useful one-dimensional separation can be achieved using high voltage electrophoresis at pH2 after conversion of the homocystine to homocystic acid by hydrogen peroxide oxidation. Normal urine gives no detectable homocystic acid, but it is quite obvious in patients with homocystinuria even at low levels of excretion.

Medical treatment

On normal diet, the patient excreted 3 mg. methionine and 18 mg. homocystine per g. urea. Plasma levels of methionine and homocystine were 1·4 and 3·0 mg./100 ml. respectively (Fig. 3, opposite).

After 2 weeks' low methionine diet (based on lentils and gelatine with cystine supplements) with pyridoxine, the plasma methionine fell to 0·8 mg./100 ml. and the plasma homocystine to 0·3 mg./100 ml.

Owing to home circumstances, it was difficult to continue dietary treatment. He was maintained for some time on 50 mg. pyridoxine/day. On this treatment, the plasma

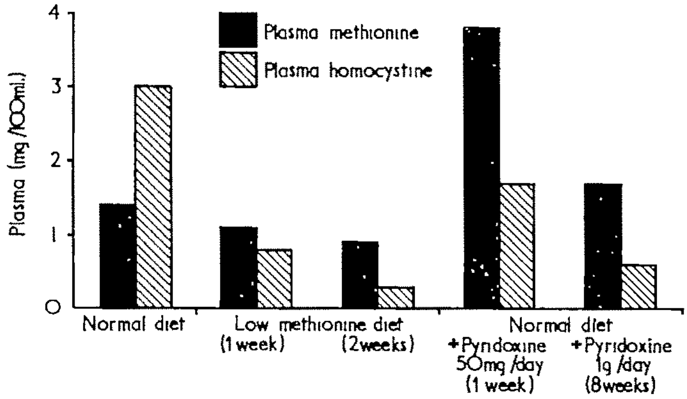

FIG. 3 *Effects of treatment on plasma methionine and homocystine*

methionine returned to 3·8 mg./100 ml., and the plasma homocystine to 1·8 mg./100 ml.

As Carson and Carré (1969) have recently recommended the use of large doses of pyridoxine, he was then given 1,000 mg./day of pyridoxine, and on this treatment the plasma methionine was maintained at 1·6 mg./100 ml. and the plasma homocystine at 0·6 mg./100 ml. Treatment with pyridoxine has thus reduced homocystine levels.

Summary

An 8½-year-old white boy with homocystinuria is described. The condition remained unrecognized until the left lens dislocated after an injury. The diagnosis of homocystinuria should be borne in mind even when the lens appears to dislocate because of trauma.

The lens was removed but the eye remained blind because of optic atrophy. The aetiology of optic atrophy in homocystinuria is discussed.

The boy survived six operations without thrombosis, although he had vasculitis.

The progressive nature of genu valgum in homocystinuria is described.

Pyridoxine, 1,000 mg./day considerably reduced the plasma homocystine levels.

This patient was under the care of Mr. A. Stanworth, to whom we are grateful for permission to publish case details and for helpful comments in the preparation of this paper.

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Addendum

December 11, 1969 The right lens dislocated spontaneously into the anterior chamber. The patient was placed flat in bed and given Diamox 125 mg. twice daily. The pupil was dilated with gutt. Phenylephrine 10 per cent. and after one day the lens replaced itself behind the iris. The pupil was immediately constricted with gutt. Pilocarpine 4 per cent. and is now permanently miosed with the aid of gutt. Pilocarpine 2 per cent. three times a day. The visual acuity has fallen to less than 6/60 in this eye with −5 D.sph.

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Causes of enucleation in Uganda

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This review is presented for the following reasons:

(1) It seems important to know the causes of conditions in which less drastic treatment had to be abandoned.

(2) The pattern of eye diseases in different parts of the world is not easily ascertained, but the causes of enucleations are usually recorded and available, and may give information on the relative frequency of different pathological conditions.

(3) Few reports on this subject have hitherto been published (Ammann, 1962).

Material

The following data have been collected from Mulago Hospital, Kampala, Uganda. This is the main hospital in Uganda, and is the clinical teaching centre of the Medical School of Makerere University College. The Eye Department has 36 beds, and there are six other smaller eye units in Uganda. Most of our cases come from areas near the hospital, *i.e.* from Buganda, although some come from other regions. Our cases were unselected, and it was our aim to include all enucleations in this part of Uganda for the 5 years 1963 to 1967. Altogether 207 eyes were removed by enucleation, evisceration, or (in a few cases of malignant tumour) exenteration of the orbit. All were treated as in-patients. The indications for enucleation in this series do not differ from what is generally accepted in most clinics.

Findings

RELATIVE FREQUENCY OF ENUCLEATION

The number of enucleations has been calculated as a percentage of all out-patients, in-patients, and eye operations on in-patients in the Eye Department of Mulago Hospital in the 5 years under review. The results are given in Table I (opposite), which also shows comparable figures from Basel and Berlin (Amman, 1962).

Enucleations, expressed as a percentage of in-patients and of operations, are much more frequent in Mulago Hospital than in Basel 1950-54 and 1935-39 and in Berlin 1925-35.

CAUSES OF ENUCLEATION

We are here mainly interested in the *primary* cause, *i.e.* the *aetiology* of the condition leading to removal of the eye. The *immediate* cause, *i.e.* the condition of the eye immediately before enucleation, may be less interesting. In most cases the primary cause was easy to

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Table I *Cases of enucleation as percentage of patients and operations compared with figures from Basel and Berlin*

Cases	*Mulago Hospital* 1963–67		*Basel*		*Berlin*
	Total new cases	*Percentage enucleations*	1935–39	1950–54	1925–35
Out-patients	105,984	0·2	0·5	0·2	0·5
In-patients	3,837	5·4	4·7	2·0	
Eye operations	2,453	8·4	7·2	3·4	5·6

ascertain *e.g.* trauma or malignant tumour, but in some the aetiology was uncertain, *e.g.* painful blind eye or phthisis bulbi. The cases were classified into seven groups, shown in Table II by sex and in order of frequency. The relative importance of the different reasons for enucleation is shown in Fig. 1.

Table II *Causes of enucleation by diagnosis and sex in order of frequency*

Diagnosis	*Total*		*Males*		*Females*		*Male : female ratio*
	No.	*per cent.*	*No.*	*per cent.*	*No.*	*per cent.*	
(1) Trauma	105	50·7	67	50·8	38	50·7	1·8 : 1
(2) Corneal disease	38	18·4	20	15·2	18	24·0	1·1 : 1
(3) Painful blind eye	19	9·2	14	10·6	5	6·7	2·8 : 1
(4) Malignant tumour	14	6·7	10	7·6	4	5·4	2·5 : 1
(5) Panophthalmitis	13	6·3	7	5·3	6	8·0	1·2 : 1
(6) Glaucoma	12	5·8	10	7·6	2	2·7	5·0 : 1
(7) Phthisis bulbi	6	2·9	4	3·0	2	2·7	2·0 : 1
Total	207	100·0	132	100·1	75	100·2	1·8 : 1

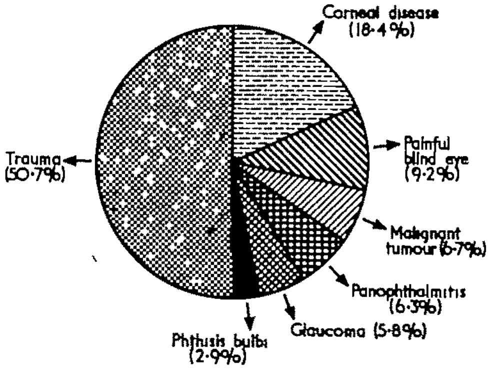

FIG. 1 *Frequency of causes of* 207 *cases of enucleation in Kampala, Uganda*

(1) *Trauma*

Here the aetiology is clear, but this group also includes cases of panophthalmitis or painful blind eye at the time of enucleation, if a traumatic aetiology was evident. Trauma was the cause of more than half the enucleations in both males and females. Serious eye injuries appear to be more frequent in Uganda than elsewhere, many being sustained in fighting. The condition of the injured eye becomes worse because most of the patients do not come to the hospital for proper treatment until many days or weeks after the accident.

(2) *Corneal disease*

This group of 38 cases was mainly comprised of perforating corneal ulcers with such complications as iris prolapse, endophthalmitis, or staphyloma. Three main factors contribute to the frequency of corneal ulcers as a cause of enucleations.

(i) The patients come late for treatment, often several weeks after the onset of the disease and after the ulcer has perforated.

(ii) Trachoma complicated by entropion and trichiasis is fairly common in this part of Uganda.

(iii) Corneal resistance to bacterial infection may be reduced in some cases by malnutrition (Kuming and Politzer, 1967; Emiru, 1968).

(4) *Malignant tumour*

This led to removal of the eye in fourteen cases (6·7 per cent.) in which the diagnosis was verified by histological examination. This percentage is considerably lower than reported by Ammann (1962) from Basel, where malignant (and suspected malignant) tumour accounted for 15 to 30 per cent. of all enucleations.

An interesting factor contributing to this difference is the histological diagnosis: seven of our fourteen cases of malignant tumour were retinoblastomas, five were squamous cell carcinomas originating from the limbus and conjunctiva, one was an orbital rhabdomyosarcoma, and one was an orbital squamous cell carcinoma originating from the maxillary sinus. There were no cases of malignant melanoma, which in Ammann's series amounted to 54 per cent. of the enucleations caused by malignant tumour. This supports the observation that intraocular malignant melanoma is rare in Africans (Templeton, 1967).

Squamous cell carcinoma originating from the limbus is frequently seen in our patients. Besides the advanced cases leading to enucleation, we have seen many early precarcinomatous tumours of the limbus and cornea. These tumours are usually pigmented, and are always situated in the palpebral aperture lateral or medial to the cornea. Exposure to sunlight of the partly pigmented conjunctiva and limbus probably plays a role in the aetiology.

(5) *Panophthalmitis*

This caused the removal of the eye in 6·3 per cent. of cases. No external cause was found, and the infection was thought to have spread from the infected ulcers, which are very common in this population especially on the legs and feet.

(6) *Glaucoma*

This included cases of primary glaucoma, those of obviously secondary glaucoma being excluded.

AGE AND SEX DISTRIBUTION

The age and sex distribution of these patients is set out in Table III and Fig. 2 (opposite). The highest number of enucleations occurs in the age group 30 to 40 years. Trauma is an even more frequent cause of enucleation in this age group than in the series as a whole (63 per cent.).

Table III *Age and sex distribution of cases of enucleation by diagnosis*
In brackets: Percentage in each age group, and sex (male + female)

Diagnosis	*Age group (yrs)*							
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+
Trauma	8 (31%) (5 + 3)	15 (56%) (6 + 9)	19 (59%) (12 + 7)	30 (63%) (21 + 9)	16 (57%) (12 + 4)	9 (53%) (7 + 2)	3 (19%) (3 + 0)	5 (38%) (1 + 4)
Corneal disease	6 (23%) (4 + 2)	4 (15%) (3 + 1)	7 (22%) (3 + 4)	8 (17%) (3 + 5)	4 (14%) (1 + 3)	3 (18%) (2 + 1)	5 (31%) (3 + 2)	1 (8%) (1 + 0)
Painful blind eye	2 (8%) (1 + 1)	4 (15%) (1 + 3)	5 (16%) (5 + 0)	2 (4%) (2 + 0)	3 (11%) (3 + 0)	1 (6%) (0 + 1)	2 (13%) (2 + 0)	0
Malignant tumour	7 (7%) (5 + 2)	0	0	1 (2%) (0 + 1)	1 (4%) (1 + 0)	2 (12%) (2 + 0)	0	3 (23%) (2 + 1)
Panophthalmitis	1 (4%) (0 + 1)	2 (7%) (0 + 2)	0	4 (8%) (4 + 0)	1 (4%) (0 + 1)	2 (12%) (1 + 1)	2 (13%) (1 + 1)	1 (8%) (1 + 0)
Glaucoma	1 (4%) (1 + 0)	1 (4%) (1 + 0)	0	2 (4%) (2 + 0)	2 (7%) (2 + 0)	0	3 (19%) (1 + 2)	3 (23%) (3 + 0)
Phthisis bulbi	1 (4%) (0 + 1)	1 (4%) (0 + 1)	1 (3%) (1 + 0)	1 (2%) (1 + 0)	1 (4%) (1 + 0)	0	1 (6%) (1 + 0)	0
Total	26 (101%) (16 + 10)	27 (101%) (11 + 16)	32 (100%) (21 + 11)	48 (100%) (33 + 15)	28 (101%) (20 + 8)	17 (101%) (12 + 5)	16 (101%) (11 + 5)	13 (100%) (8 + 5)
Male : female ratio	1·6 : 1	0·7 : 1	1·9 : 1	2·2 : 1	2·5 : 1	2·4 : 1	2·2 : 1	1·6 : 1

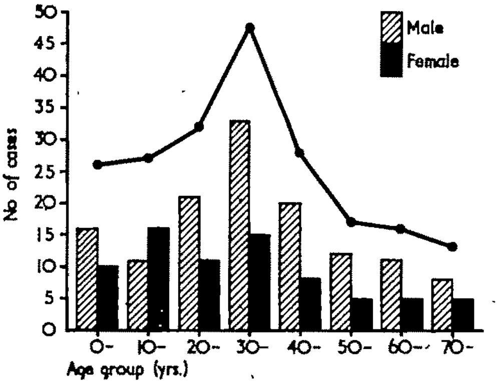

FIG. 2 *Age and sex distribution of 207 cases of enucleation in Kampala, Uganda*

There are 1·8 times as many enucleations in males as in females, and there are more male cases in every group, including the malignant tumours and glaucoma.

The predominance of males cannot be explained by a selection of male cases, as the numbers of men and women in the out-patients clinic is about equal.

Summary

The primary causes of 207 enucleations in Kampala, Uganda, are reviewed. The cases are classified in seven aetiological groups. Trauma is the cause of more than half the enucleations, and the next in importance is corneal disease (18·4 per cent.). The male: female ratio is 1·8, and in adults over 20 years of age 2·1.

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Experimental ocular leishmaniasis

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An experimental study has been made of the ocular lesions produced by *Leishmania donovani* infection. Animals were injected with *Leishmania donovani* subconjunctivally, into the anterior chamber, and into the vitreous. The ocular lesions observed experimentally were conjunctival and corneo-scleral nodules, interstitial keratitis, iridocyclitis, choroiditis, and retinitis together with vitreous haemorrhage.

Subconjunctival and retrobulbar injections of *Leishmania donovani* in hamsters produced visceral leishmaniasis; thus, besides the usual parenteral and intracardiac routes often used for infecting hamsters with *Leishmania donovani*, the ocular route can also be used.

The protozoon *Leishmania*, which is transmitted by the bite of the sandfly (*Phlebotomus*), causes three distinct clinical entities: oriental sore caused by *Leishmania tropica;* kala-azar caused by *Leishmania donovani*; and espundia caused by *Leishmania braziliensis.*

ORIENTAL SORE of the eyelids has been recorded by El Kattan (1935), Kamel (1943, 1945), Wahba (1948), El Said Kahlil Abu Shusha (1949), di Ferdinando (1950), Dobrzhanskaya (1964), and Morgan (1965).

The lid is involved only in 2·5 per cent. of cases of cutaneous leishmaniasis (Pestre, 1955), probably because the movements of the lids prevent the fly-vector from biting the skin in this region (Morgan, 1965). Fuchs (1951) described scars of the upper lid as a sequel to leishmaniasis. The conjunctiva is rarely affected in cases of oriental sore (Donatelli, 1950; Gandolfi, 1952), and conjunctivitis when present is due to secondary organisms (Scuderi, 1947). The cornea is occasionally affected by ulcerative keratitis (Chams, 1930) due to direct infection from the fingers (Duke-Elder, 1965).

KALA-AZAR has a specific affinity for the reticuloendothelial system. Various authors, including Lee (1924), Ling (1924), Bhaduri (1927), Recupero (1954), and Tassman, O'Brien, and Hahn (1960), have recorded the presence of retinal haemorrhages in patients suffering from this condition.

ESPUNDIA, naso-pharyngeal leishmaniasis or *Leishmania Americana*, produces ocular lesions in 10 to 20 per cent. of cases (Duke-Elder, 1965). It causes ulcerative granuloma in the nose, which may spread to destroy the lids and conjunctiva (Pessôa and Barreto, 1948; Azulay, 1952). The lid may be affected by way of the naso-lacrimal duct (Machado, Machado, and Moura, 1958). The cornea is often affected by interstitial keratitis (de Andrade, 1942), with aneurysmal formations constituting a leishmanian pannus (Duke-Elder, 1965).

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The diagnosis of oriental sore and espundia is made by taking a smear from the edge of the ulcer and staining it with Giesma or Leishman stain, culturing the organism on N.M.N. (Novy-MacNeal-Nicolle) medium, or by an intradermal skin test (Leishmanin test).

The diagnosis of kala-azar is made by detecting the *Leishmania donovani* bodies in smears from splenic, liver, and sternal punctures, cultures in N.M.N. medium, blood examination, and biochemical tests.

The aim of this work was to study experimentally the different ocular lesions that can develop from *Leishmania donovani* infection.

Methods

Seventeen hamsters of the "Golden Syrian type", weighing from 80 to 100 g., and fourteen guinea-pigs of the "South American type", weighing from 320 to 350 g., were used.

The "Kenya strain" of *Leishmania donovani*, which was used in all the experiments, was isolated from the spleen of infected hamsters previously injected with *Leishmania donovani* by the intracardiac route. The anaesthesia used was intraperitoneal Urethane in a dose of 1 to 2 g./kg. body weight.

The specimens removed from the animals, such as enucleated globes and internal organs such as the liver, spleen, and brain, were all fixed in formalin 10 per cent. and embedded in paraffin. Histological sections were cut at a thickness of 6μ, and stained with both haematoxylin and eosin and Giemsa stain.

The experimental work was carried out according to the following scheme:

(1) Injection of *Leishmania donovani* subconjunctivally in hamsters and guinea-pigs.

(2) Injection of *Leishmania donovani* into the anterior chamber of guinea-pigs.

(3) Injection of *Leishmania donovani* into the vitreous of hamsters and guinea-pigs.

(4) Examination of the spleen, liver, and brain of animals previously infected with *Leishmania donovani* by subconjunctival or retrobulbar injection.

(5) Examination of the eyes of hamsters previously infected with *Leishmania donovani* by the intracardiac route.

(1) Injection of Leishmania donovani *subconjunctivally in hamsters and guinea-pigs*

0·2 ml. *Leishmania donovani* (suspended in physiological saline) were injected subconjunctivally into two hamsters, and 0·4 ml. into two guinea-pigs. The left eyes only were injected, leaving the right eyes as controls. Repeated inspections for ocular lesions were made. The animals were killed after 50 days, and the lids together with the globes were removed and fixed and serial histological sections were cut.

(2) Injection of Leishmania donovani *into the anterior chambers of guinea-pigs*

0·1 ml. *Leishmania donovani* suspension was injected into the anterior chamber of the left eyes of three guinea-pigs after an equal amount of aqueous had been aspirated. The animals were examined by the slit lamp for 30, 40, and 50 days respectively; they were then killed, the globes were enucleated and fixed, and serial histological sections were cut.

(3) Injection of Leishmania donovani *into the vitreous of hamsters and guinea-pigs*

0·2 ml. *Leishmania donovani* suspension was injected into the left vitreous chambers of three hamsters and 0·3 ml. into three guinea-pigs. Repeated slit-lamp and fundus examinations were performed for 40, 50, and 60 days; the animals were then killed, the globes were enucleated and fixed, and serial histological sections were cut.

(4) *Examination of spleen, liver, and brain of animals previously infected with* Leishmania donovani *by the ocular route*

(a) AFTER SUBCONJUNCTIVAL INJECTION

Three hamsters and three guinea-pigs were used. Only two hamsters and two guinea-pigs were injected with *Leishmania donovani* subconjunctivally as described previously. The injection was unilateral in one animal, and bilateral in the other. The third hamster and guinea-pig were kept as controls. The animals were killed after 30 days, the abdomens and heads were opened, and under strict asepsis smears were made from the spleen, liver, and brain. The smears were stained by Giemsa and examined with an oil immersion lens. Histological sections were also cut and stained by haematoxylin and eosin and Giemsa stain.

(b) AFTER RETROBULBAR INJECTION

Three hamsters and three guinea-pigs were used. A retrobulbar injection of 0·3 ml. *Leishmania donovani* suspension was carried out in two hamsters and of 0·4 ml. in two guinea-pigs. The injections were made through the lower conjunctival fornices. The injection was unilateral in one animal and bilateral in the other. The third hamster and guinea-pig were kept as controls. The animals were killed after 30 days. Smears and histological sections were taken from the spleen, liver, and brain as in the previous experiment. The globes were also enucleated and fixed, and histological sections were cut.

(5) *Examination of eyes of hamsters previously infected with* Leishmania donovani *by the intracardiac route*
Six hamsters were injected with 0·3 ml. *Leishmania donovani* suspension intracardially. They were then repeatedly examined for ocular lesions by split-lamp and fundus examination for a period of three months.

Results

The subconjunctival injection of *Leishmania donovani* caused a severe conjunctival injection, with the development of conjunctival and corneo-scleral nodules (Figs 1 and 2). Interstitial keratitis was also seen by slit-lamp examination. Serial histopathological sections of the nodules showed the presence of round cell infiltration (Fig. 3). The lacrimal gland was also found to be infiltrated with round cells (Fig. 4), and *Leishmania donovani* bodies were evident in sections stained by Giemsa stain.

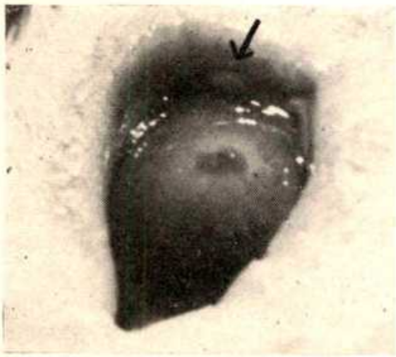


FIG. 1 *A corneo-scleral nodule in the left eye of guinea-pig after subconjunctival injection of* Leishmania donovani

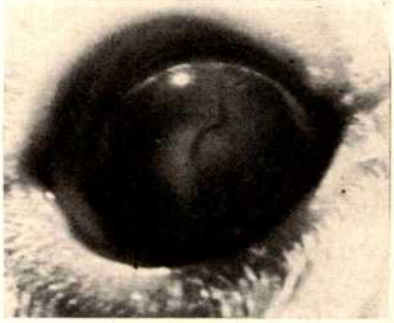
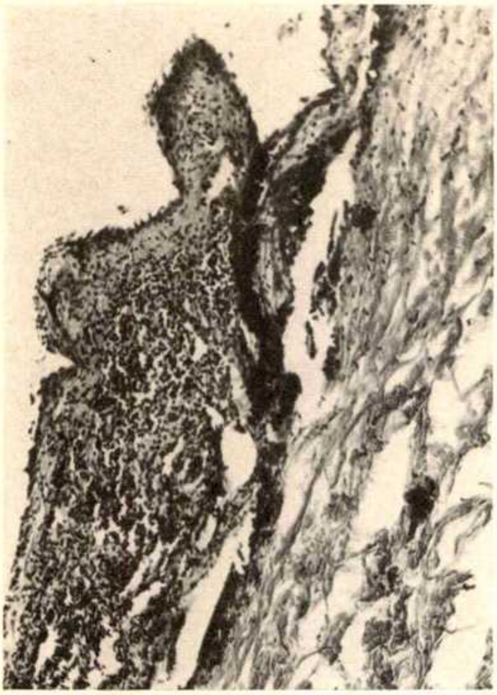


FIG. 2 *A conjunctival blood vessel crossing the corneo-scleral nodule and encroaching on the left cornea of guinea-pig after subconjunctival injection of* Leishmania donovani

Injection of *Leishmania donovani* into the *anterior chamber* of guinea-pigs caused iridocyclitis, keratic precipitates, and hypopyon. Histopathological sections revealed the presence of a round cell infiltration in the cornea, iris, and ciliary body.



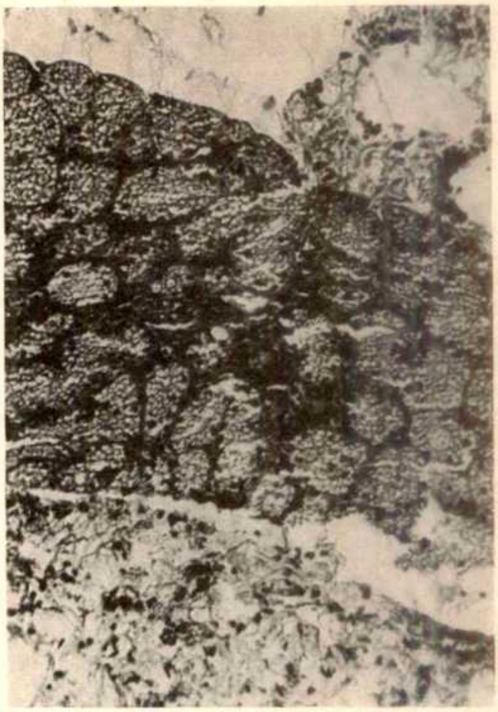


FIG. 3 *Histopathological section of a conjunctival nodule in a hamster, showing round cell infiltration after subconjunctival injection of* Leishmania donovani. ×350

FIG. 4 *Histopathological section of lacrimal gland of guinea-pig, showing round cell infiltration.* ×800

Injection of *Leishmania donovani* into the *vitreous* of hamsters and guinea-pigs caused retinitis, choroiditis, and vitreous haemorrhage. A greyish yellow-reflex developed in hamsters. Histopathological sections of the globes revealed the presence of round cells and red blood corpuscles in the vitreous (Fig. 5). The retina and choroid were also infiltrated by lymphocytes and plasma cells.

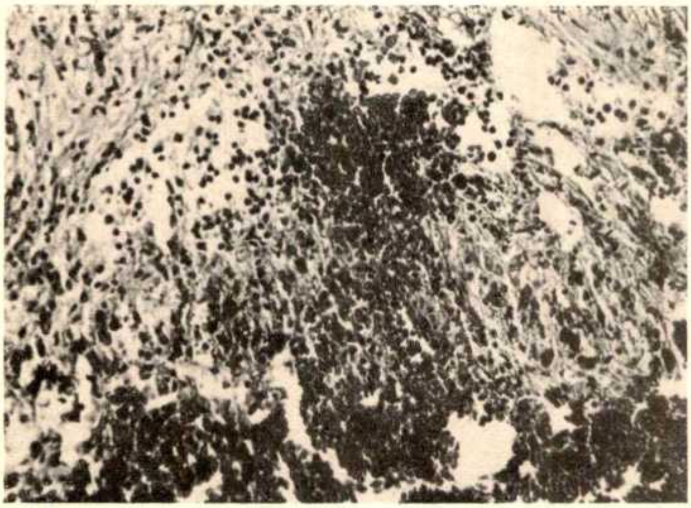


FIG. 5 *Histopathological section of vitreous chamber of hamster, showing round cell infiltration and red blood cells after injection of* Leishmania donovani. ×600

The examination of the internal organs of animals previously infected with *Leishmania donovani* by the ocular route, revealed the following results:

After subconjunctival injection

The hamsters showed a marked enlargement of the spleen 30 days after the injection, as compared with the spleen of the control hamsters (Figs 6 and 7). Smears from the spleen of the infected hamsters revealed numerous *Leishmania donovani* bodies, some in the macrophages but mostly extracellular (Fig. 8). Smears from the liver and brain also revealed *Leishmania donovani* bodies, but these were very scanty. Histopathological sections stained by Giemsa also revealed the bodies which were more numerous in the splenic sections.

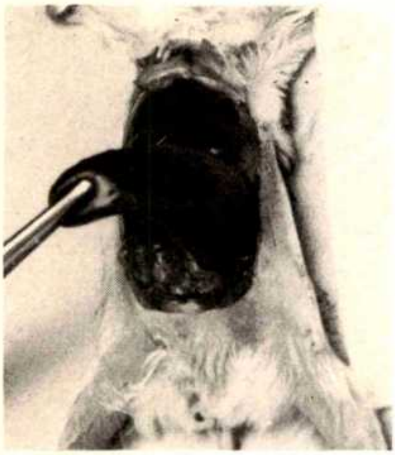


FIG. 6 *Hamster showing marked enlargement of the spleen after subconjunctival injection of* Leishmania donovani

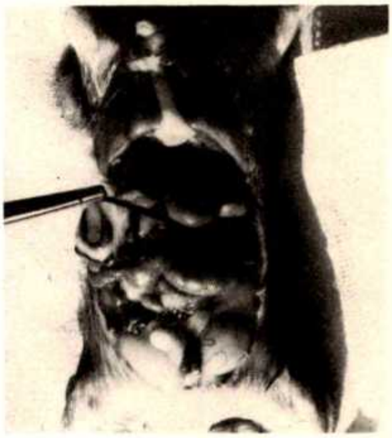


FIG. 7 *Control hamster, showing normal spleen*

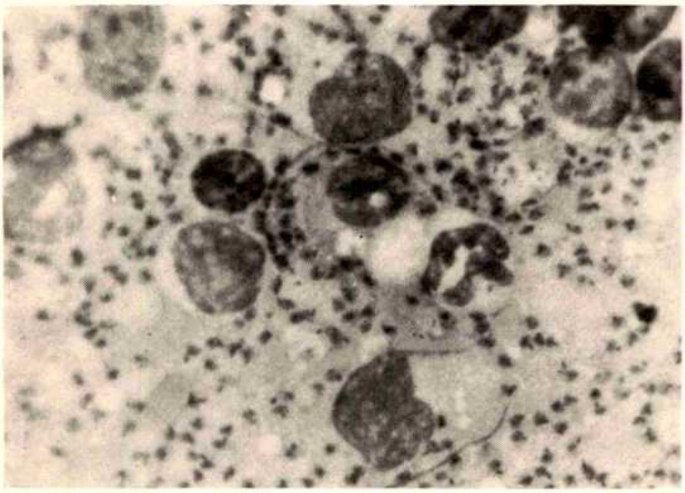


FIG. 8 *Smear from spleen of hamster, showing* Leishmania donovani *bodies in the macrophages, but mostly extracellularly after subconjunctival injection of* Leishmania donovani. *Oil immersion* ×4,850

The guinea-pigs injected subconjunctivally with *Leishmania donovani* did not show any evidence of such bodies in smears from the spleen, liver, or brain. A culture from the spleen on N.M.N. medium was performed, but also proved negative.

After retrobulbar injection

The hamsters also showed a marked enlargement of the spleen 30 days after the injection, as compared with the control animal. *Leishmania donovani* bodies were also evident in smears and histopathological sections of the liver and brain, as in the previous experiment. The organs from the guinea-pigs were also unaffected. The retrobulbar injection did not affect the animal's eyes, except for a mild conjunctival injection with mucous discharge.

It was noticed that the hamsters which were bilaterally injected, whether by the subconjunctival or retrobulbar route, showed a severer infection than those injected in one eye only.

The examination of the eyes of hamsters previously infected with *Leishmania donovani* through the *intracardiac route* showed that only two of six hamsters infected with visceral leishmaniasis or kala-azar developed ocular lesions. Ciliary injection, aqueous flare, and interstitial keratitis developed in the right eye of one of the hamsters 50 days after the injection. It was difficult to examine the lens and fundus because of the corneal lesion. The animal died 8 days later from kala-azar. The second hamster developed bilateral lesions. A corneo-scleral nodule was noticed in the right eye 2 months after the injection. An interstitial keratitis developed later and the whole cornea was opaque by the third month. The left cornea also showed an interstitial keratitis 9 days after the appearance of the right nodule. The cornea became gradually opaque, and the animal died 3 months after the injection from kala-azar.

Discussion

Reviewing the literature on the subject of ocular leishmaniasis, Metelkin (1928) found that corneal lesions could be produced experimentally in dogs; an interstitial keratitis was produced with the presence of the parasites in the cornea.

Bollinger and Macindoe (1950) injected the "Australian opossum" parentally with the blood of Indian patients suffering from kala-azar. Ocular lesions were produced in the form of interstitial keratitis, iritis, cyclitis, complicated cataract, choroiditis, retinopathy, and papillitis.

Manson-Bahr (1954), discussing the ocular lesions in kala-azar, stressed the findings of Wright who showed that retinal haemorrhages occurred in the posterior segment similar to those seen in malaria. Such haemorrhages were attributed by Recupero (1954) to vascular fragility, a low platelet count, and a prolonged prothrombin time.

Sorsby (1963) stated that retinal haemorrhages in kala-azar were probably due to anaemia. He discussed the condition of "post kala-azar dermal leishmaniasis", where small vascularized nodules occasionally appear in the episclera close to the limbus. The nodules may extend to the cornea which becomes opaque and infiltrated, showing superficial and deep vascularization.

In our experimental study on ocular leishmaniasis, we observed that subconjunctival injection of *Leishmania donovani* in hamsters and guinea-pigs produced conjunctival and corneo-scleral nodules together with interstitial keratitis. The lacrimal gland was also affected.

Visceral leishmaniasis developed after subconjunctival and retrobulbar injections of *Leishmania donovani* only in hamsters, as guinea-pigs have been found to be poor hosts for *Leishmania*.

Injection of *Leishmania donovani* into the anterior chamber and vitreous of animals caused signs of iridocyclitis, choroiditis, and retinitis, together with vitreous haemorrhage.

Intracardiac injections with *Leishmania donovani* produced corneo-scleral nodules and interstitial keratitis in only some of the animals injected.

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Serious ophthalmological complications in the Ehlers-Danlos syndrome

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The main features of the Ehlers-Danlos syndrome (EDS) are cutaneous hyperextensibility, articular laxity, and fragility of the tissues. Systemic ramifications may lead to orthopaedic, cardiovascular, and gastrointestinal problems.

Minor ophthalmological changes, including epicanthic folds, strabismus, and myopia are not infrequent, but serious ocular complications are rare. However, there have been a few reports of patients with impaired vision from retinal detachment or displacement of the lens.

The EDS is a generalized disorder of connective tissue, which is usually inherited as a dominant trait. There is some scanty evidence to indicate the existence of an uncommon recessive form, and it is of great interest that the majority of the reports of sight-threatening lesions have pertained to individuals who could well have had this genetic background.

The purpose of this paper is to describe an affected brother and sister who both became blind from bilateral ocular catastrophes. The transmission of the EDS in their kindred was consistent with recessive inheritance of the trait.

Case reports

Case 1, a white male, weighed 6 lb. 3 oz. at birth in 1915. Hypermobility of the finger joints was apparent in early childhood, but apart from a tendency to skin-splitting and a moderate myopia, he was quite well until the age of 19 years. He then developed a left-sided hemiplegia, which was attributed to an intracranial bleed, consequent upon a head injury which had occurred 3 weeks previously. Considerable recovery of function took place, but some weakness of the left arm and leg persisted.

At the age of 22 years, 3 years after this event, he was struck in the right eye by a rubber patch from a car tyre. Although the blow was of no great severity, the globe of the eye was ruptured. Primary suture was performed but vision was lost, and the eye was later enucleated and replaced by a prosthesis.

He remained in good health until the age of 51, when he tripped in his home and banged the left side of his head on the ground. The globe of the left eye was ruptured and although the scleral tear was sutured, he remained blind.

A younger sister also had the EDS, and she too became blind in early adult life (*vide infra*). His other six sibs were normal, as were his parents and his own four children. There was no known consanguinity, and no other members of the kindred were affected (Fig. 1, overleaf).

Examination

In 1969 he was found to be a thin, tense man, 70 in. tall and weighing 160 lb. His elbows, knees, and shins bore hyperpigmented papyraceous scars, and he had considerable extensibility of the skin. The finger and wrist joints were very lax, and he had a moderate increase in the range of movements

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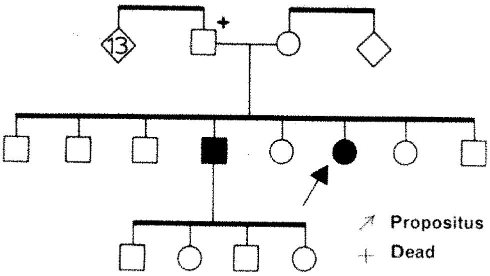

FIG. 1 *Pedigree of the patients' kindred. Affected members shown in black*

of his elbow and knee joints. Molluscoid pseudotumours were present over both elbows, and hard subcutaneous spheroids could be palpated in the shins and forearms. The left eye was false, while the right eye was shrunken and deformed, with opacity of the media. Residual signs of a left-sided hemiplegia could be elicited, but the physical examination was otherwise unremarkable.

Case 2, the sister of Case 1, weighed 6 lb. at birth in 1924. She had bilateral talipes equinovarus deformities of the feet, which were corrected surgically at the age of 12. A thoraco-lumbar kyphoscoliosis appeared when she was 8 years old, and in spite of treatment by prolonged traction during adolescence, the deformity persisted (Fig. 2). In recent years she has worn a spinal brace for troublesome backache. Frequent dislocations of both shoulders and subluxations of the right patella took place during childhood. These were always easily reducible and the liability to these complications diminished as she reached adult life. Her bony prominences became scarred from the frequent lacerations which occurred on minor trauma and her shins were discoloured by recurrent bruises (Fig. 3).

She required a transfusion of 3 pints of blood for a haematemesis which occurred when she was 30 years old. A duodenal ulcer was demonstrated by barium studies at this time, and her continuing dyspepsia was treated with antacids. Melaena occurred 3 years later, but the gastrointestinal symptoms then resolved. An episode of dysphagia at the age of 44 was attributed to oesophageal spasm associated with acid reflux and a hiatus hernia. Conservative treatment brought symptomatic relief. When she was in her early forties, cystic masses were removed from each breast at uneventful operations.

Ocular problems began at the age of 6, when she was given spectacles for severe myopia associated with a divergent strabismus of the right eye. Episodes of visual disturbance led to the diagnosis of congenital glaucoma when she was 27 years old, and in a brief case report, Durham (1953) mentioned that she had microcornea and blue sclera. Daily treatment with 2 per cent. pilocarpine kept her intraocular pressure at a normal level, and apart from a minor bilateral visual field loss, she had no further eye trouble for 10 years.

At the age of 36, however, she suddenly lost the sight of the left eye. A detachment of the retina was diagnosed and an unsuccessful repair operation was carried out one month later. The surgeons commented upon the fragility of the sclera and the amount of bleeding which occurred during this procedure.

In the following year, detachment of the right retina took place. Repair by light coagulation was successful, but a further detachment occurred 6 months later. Surgical intervention did not bring about any improvement, and she subsequently remained totally blind.

Examination

In 1969 she was found to be a good-natured intelligent blind lady, 64 in. tall and weighing 130 lb. A marked thoraco-lumbar kyphoscoliosis was present and her feet and breasts bore operation scars. She had scarring, articular laxity, and cutaneous hyperextensibility which resembled the stigmata borne by her brother, both in distribution and in degree. Her left eye was misshapen with an atrophied iris and a dense cataract, while similar but less marked changes were present in the right eye. No abnormality was detected in any other system.

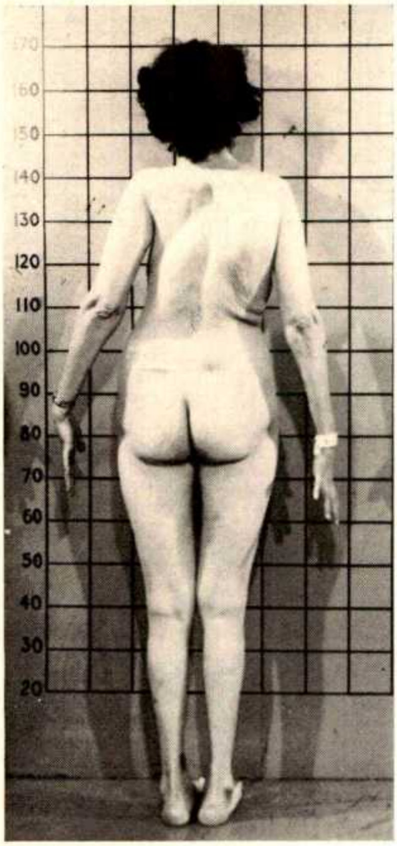

FIG. 2 *Case 2. Thoraco-lumbar kyphoscoliosis*

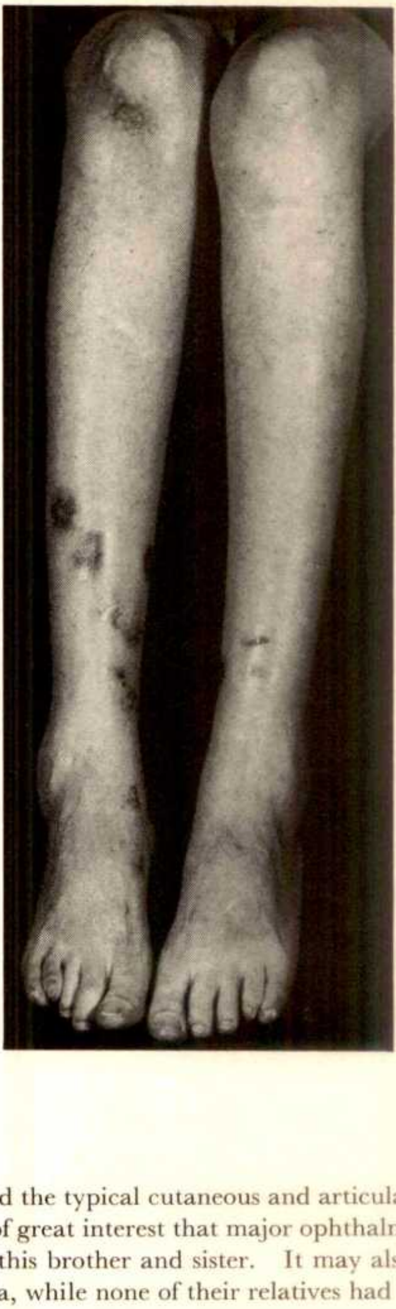

FIG. 3 *Case 2. Wide hyperpigmented papyraceous scars over bony prominences of the legs*

Discussion

There is no doubt that these two patients had the typical cutaneous and articular stigmata of the EDS, in a moderate degree, and it is of great interest that major ophthalmic calamities, leading to total blindness, occurred in this brother and sister. It may also be significant that both of them initially had myopia, while none of their relatives had any ocular problems.

Although minor ophthalmological abnormalities are common in the EDS, major ocular complications are very infrequent. In a series of 100 affected patients, 27 had epicanthic folds, seven had blueness of the sclera, seven had strabismus, and eight had myopia, while redundant skin on the upper eyelids, ease of eversion of the upper lid (Méténier's sign), and widely-spaced eyes were frequently encountered. None of the patients in this series had any serious ophthalmological lesions (Beighton, 1968a).

Table *Previous reports of serious ophthalmological complications in patients with the Ehlers-Danlos syndrome*

Authors	*Date*	*Patient*		*Ocular lesion*	*Family history*	*Comment*
		Sex	*Age (yrs)*			
Thomas and others	1953	F	2	Blue sclera Keratoconus Abnormal scleral fragility Corneal damage on minor trauma	Brother affected Parents normal but consanguineous	
Bossu and Lambrechts	1954	F	19	Blue sclera Myopia Right retinal detachment and proliferating retinitis Left macular degeneration and spontaneous vitreous haemorrhage	12 sibs 2 affected with EDS Parents and other members of the kindred were normal	
Cordella and Vinciguerra	1966	M	30	Blue sclera Right retinal detachment Left displacement of lens, with iridodonesis	8 sibs 2 affected with EDS Parents normal but consanguineous	
Durham McKusick Pemberton and others	1953 1966 1966	F		Blue sclera Myopia Bilateral retinal detachment Fragile ocular tissue	Affected brother (Case 1) 6 normal sibs Normal parents	Case 2 in present paper
Thomas and others	1952	M	48	Dislocated lenses Fragile ocular tissues at operation		Probably not true EDS
Frieden and others	1962	M	46	Retinal detachment Died from ruptured aortic valve cusp	Affected children	Probably not true EDS
Pemberton and others	1966	M	42	Retinal detachment Died from dissected aorta	Affected children	Probably same condition as Frieden's case

There have been very few reports of grave ocular complications in affected patients (Table). Thomas, Neimann, Cordier, and Algan (1963) treated a 2-year-old girl who suffered corneal damage after a minor blow to the head. They noted that she had blue sclera, keratoconus, and undue scleral fragility. Her brother also had the EDS and her parents, who were normal, were consanguineous. Bossu and Lambrechts (1954) described an affected 19-year-old girl, who had a detached retina and proliferating retinitis in the right eye and macular degeneration and spontaneous vitreous haemorrhage in the left. She had twelve sibs, two of whom showed the EDS. Her parents and the other members of the kindred were normal, and there was no consanguinity. Cordella and Vinciguerra (1966) reported a 30-year-old man, with the typical stigmata of the EDS, who had thin blue sclera, a right-sided retinal detachment, and displacement of the lens of the left eye. His eight sibs were normal, while two others had been stillborn. His parents were first cousins. In view of their family histories, it is possible that each of these patients inherited the EDS as a recessive trait.

Durham (1953), Pemberton, Freeman, and Schepens (1966), and McKusick (1966) all mention Case 2 of the present report, but there do not seem to be any other descriptions of serious ocular lesions in individuals with the genuine EDS. Exophthalmos due to an intracranial arterio-venous fistula was described by François, Woillez, Warrot, and Maillet (1955) and similar events have been reported by Graf (1965) and Bannerman, Graf, and Upson (1967). This complication has a vascular rather than an ocular basis, and represents a further uncommon complication of the syndrome.

Thomas, Cordier, and Algan (1952) discussed a 48-year-old man with dislocated lenses, in whom corrective surgery was made difficult by the fragility of the ocular tissues. No members of his kindred were similarly affected. Frieden, Hurwitt, and Leader (1962) reported a 46-year-old man with retinal detachments who died of an aortic lesion, and Pemberton and others (1966) described a large kindred of loose-jointed individuals, in one of whom retinal detachment and dissection of the aorta occurred. However, from the case descriptions, it seems likely that all of these patients had an unusual undelineated connective tissue disorder rather than the true EDS.

From the genetic standpoint, the EDS is usually transmitted as a dominant trait, although an X-linked form has been described (Beighton, 1968b). McKusick (1966) suggested that the EDS might be heterogeneous, and Barabas (1967) and Beighton, Price, Lord, and Dickson (1968) were able to distinguish several clinically distinct dominant types of the disorder. There is no firm evidence for a recessive form of the EDS, but Capotorti and Antonelli (1966) investigated affected sibs in a kindred with a major degree of consanguinity, while Ronchese (1936), Tobias (1934), and Johnson and Falls (1949) also reported affected offspring of consanguineous marriages. Sporadic cases of the EDS are not uncommon, and while many of them probably represent new dominant mutations, it is possible that some of them are homozygotes for a recessive trait. Similarly, there have been several instances of affected sibs with normal parents. Incomplete penetrance of the gene could account for this finding, but recessive inheritance is another possibility.

The fact that Case 1 had four normal children, an affected sister, normal parents, and six other normal sibs is suggestive of recessive inheritance. It is remarkable that, in addition to Cases 1 and 2 above, all three other reported patients with serious ocular complications had pedigrees which were consistent with recessive inheritance.

Genetic heterogeneity has been demonstrated in many familial disorders, and on this basis, there is an adequate precedent for a recessive form of the EDS. If a recessive form of the EDS does indeed exist, it appears that the phenotypic features are those dermal and joint changes which are usually found in the EDS of moderate severity, with the addition of a liability to serious ocular complications. Blueness of the sclera and myopia might be additional features of this uncommon recessive ophthalmological form of the EDS.

Summary

A brother and sister with the typical cutaneous and articular manifestations of the Ehlers-Danlos syndrome both lost their sight after ocular catastrophes. Their pedigree was consistent with autosomal recessive inheritance.

Other patients have been reported with similar stigmata of the EDS, who experienced serious ocular complications, and in whom there was considerable evidence to indicate a recessive mode of inheritance of the condition.

It is possible that there is a distinct ophthalmic form of the EDS, in which fragility of the ocular tissues predisposes to serious ophthalmological complications.

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Modifications of Scheie's operation

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In recent years Scheie's operation (Scheie, 1958) has been frequently performed because of its relatively simple technique. The results have been mainly satisfactory in bringing the intraocular pressure to normal in cases of glaucoma. Nevertheless filtration is not always well maintained, for various reasons:

(1) Excessive scarring of the conjunctival flap causing closure of the limbal fistula.

(2) Exuberant Tenon's capsule, especially in young patients.

(3) Blockage of the fistula from within by tags of iris, ciliary processes, vitreous, and occasionally the lens.

(4) Re-operations in which the fistula is more prone to closure.

In a study of the results in fifty eyes in which Scheie's operation was performed in the past 5 years, it was found that it was necessary to resume full medical treatment or even to re-operate to control the glaucoma in the majority of cases. It was therefore felt necessary to modify the technique of Scheie's operation, and procedure has been classified into four types, I, II, III, and IV, depending upon the site of the operation in the limbal area. In any particular case the procedure adopted is determined by the following factors:

(1) RATE OF PROGRESSION OF FIELD LOSS

When this is very rapid and severe, the postoperative intraocular pressure should be reduced well below the average readings.

(2) DEGREE OF EXCAVATION OF OPTIC DISC (CUP : DISC RATIO)

The greater the extent of cupping, the more generous the drainage should be at the limbal fistula.

(3) AGE

Younger patients present exuberant Tenon's capsule and a greater degree of vascularity in the episcleral tissues.

(4) PREOPERATIVE DEPTH OF ANTERIOR CHAMBER and NATURE OF THE ANTERIOR CHAMBER ANGLE

(5) WHETHER THE OPERATION IS PRIMARY OR IS A RE-OPERATION

The basis for typing is the anatomy of the limbus and the angle of the anterior chamber. The limbus is not a line but an area 1·5 to 2 mm. wide. Posteriorly it is limited by a shallow corneo-scleral sulcus and it ends at the conjunctival reflection anteriorly. To achieve a permanently functioning filtration, it is important to select an appropriate site for operation on the limbal area. It is this crucial step which brings success or failure to the whole operation.

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Type I (Classical Scheie's operation: Fig. 1)

The incision is made 1 mm. behind the limbal area. A vertical incision at this site enters the angle recess in its narrowest posterior part. This incision is therefore prone to be easily blocked from within or from outside because of its close proximity to the vascular episcleral and scleral tissue. Because it opens into the narrowest part of angle recess, it can be blocked by iris or ciliary process, vitreous, or lens, especially in eyes with a narrow angle and a very shallow anterior chamber.

Indications for this operation are very few. It should be performed only in cases which need minimal drainage and have a deep anterior chamber with wide angles.

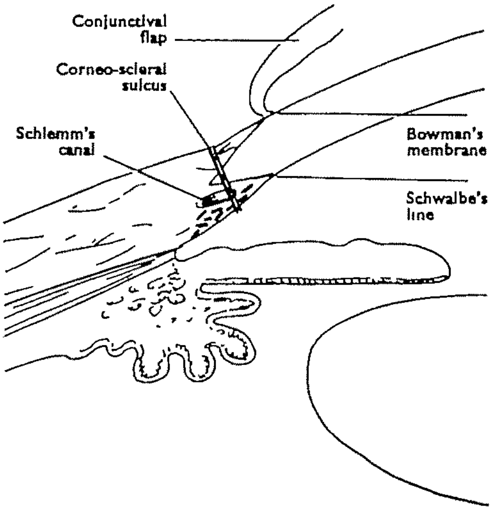

FIG. 1 *Scheie's operation. Incision through corneo-scleral sulcus into Schlemm's canal (Type I)*

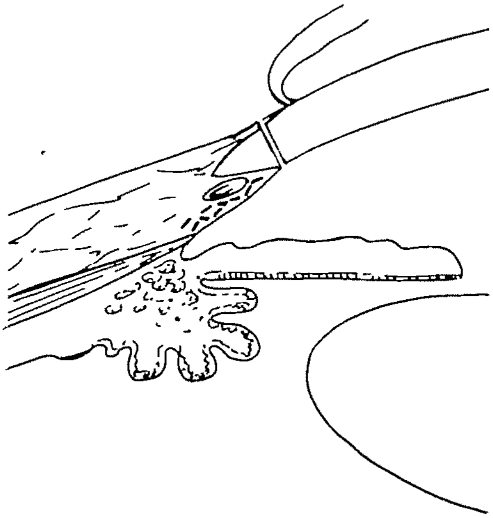

FIG. 2 *Incision through anterior and posterior margins of limbus (Type II)*

Type II (Fig. 2)

The incision is made midway between the corneo-scleral sulcus and the conjunctival reflection. This incision is more efficient because it is sited further forward from the vascular scleral and episcleral tissue and the internal opening lies at a reasonable depth in the anterior chamber.

This type should replace the classical Scheie's operation in eyes with a deep anterior chamber and wide angles and in which Tenon's capsule is thin and scanty. A shallow anterior chamber with a narrow angle is a contraindication.

Type III (Fig. 3)

The incision is made immediately behind the conjunctival reflection at the extreme anterior edge of the limbal area. The drainage bleb encroaches rather on the corneal side. Corneal tissue heals more slowly than the vascular conjunctival and episcleral tissue, so that the conditions are more favourable for the formation of fistula and a functioning bleb.

This type should be used in cases of uncontrolled glaucoma with a shallow anterior chamber and narrow angles, and in young patients where Tenon's capsule is vascular and thicker. This last factor is one of the common causes of failure to achieve a draining fistula.

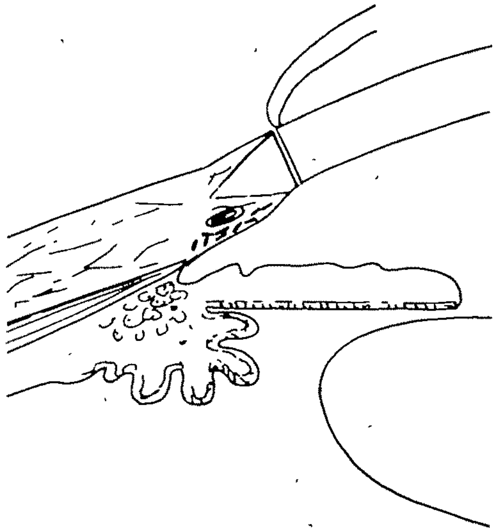

FIG. 3 *Incision at anterior limit of limbus. Danger of "button-holing" conjunctival flap (Type III)*

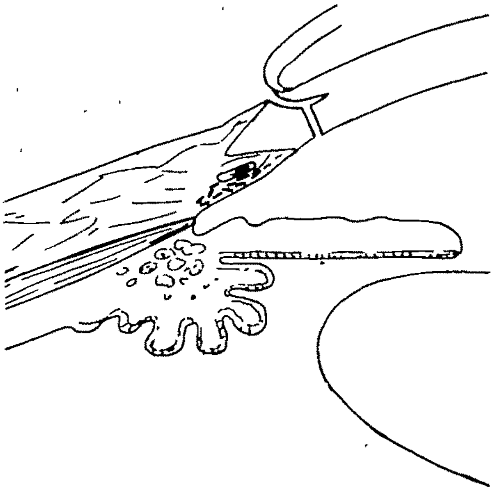

FIG. 4 *Incision through posterior layer of split cornea (Type IV)*

Type IV (Fig. 4)

The aim of this operation is to achieve a greater outflow which is the vital factor for success in certain types of glaucoma. The cornea is split into two layers starting at the conjunctival reflection at the anterior limit of limbal band. The incision to enter the anterior chamber is carried through the posterior layer of the split cornea. Great care is taken to avoid conjunctival "button-holing". The drainage site in this case would be more or less corneal. The postoperative bleb tends to be diffuse and multiloculated, but it is more effective in attaining the correct level of postoperative intraocular pressure.

The indications for this type are as follows:

(1) A very wide cupped optic disc.
(2) Juvenile glaucoma.
(3) An extremely shallow anterior chamber.
(4) Re-operations.
(5) Congenital glaucoma.
(6) Pigmentary glaucoma.
(7) "Low tension" glaucoma.
(8) In the coloured races the conventional drainage operations are often not very successful because excessive fibrosis closes the fistula.

Results

The results obtained in a series of fifty eyes in the past 5 years are shown in Table I (overleaf). Eyes with less than 6 months' follow-up are not included.

Each eye was assessed preoperatively by careful measurements of the anterior chamber, and a gonioscopic view of the angle; other factors already mentioned were taken into account in selecting the type of Scheie's operation. In all cases operative treatment was indicated because of uncontrolled intraocular pressure, field loss, or both.

Fifteen eyes had a deep anterior chamber with wide angles and a Scheie's Type I operation was performed; eight still required treatment and four were uncontrolled.

Seventeen eyes had a rather shallow anterior chamber with iris *bombé* appearance and a narrow to medium angle. These eyes were operated by Scheie's Type II; only four still required treatment postoperatively.

In ten eyes with chronic closed-angle glaucoma, and a shallow anterior chamber with narrow angles, a Scheie's Type III procedure was carried out; all but two were controlled without further treatment.

Scheie's Type IV operation was performed in the following eight cases; all were controlled without further treatment:

(1) A previous glaucoma operation was not functioning efficiently (3)
(2) Thrombotic glaucoma with abnormal vessels in the angle (1)
(3) Secondary glaucoma (1)
(4) Low tension glaucoma (1)
(5) Pigmentary glaucoma (1)
(6) Chronic simple glaucoma, with a shallow anterior chamber and a very narrow angle (1)

Table I *Diagnosis in fifty cases of glaucoma requiring surgery*

Type of glaucoma	*No. of eyes*
Chronic simple	32
Chronic closed-angle	14
Thrombotic	1
Secondary	1
"Low tension"	1
Pigmentary	1

Table II *Type of operation and results*

Type	*No. of eyes operated*	*Results*		
		Controlled without treatment	*Controlled with treatment*	*Uncontrolled*
I	15	13	8	4
II	17	13	4	0
III	10	8	2	0
IV	8	8	0	0

The postoperative results are tabulated in Table II. Intraocular pressure was considered to be normal postoperatively if the reading was 24 mm. Hg or less by applanation, whereas a Schiötz reading of 30 mm. Hg was regarded as controlled by Scheie (1958).

The Table shows that filtration blebs sited anteriorly are more successful and function better, as the circumstances are more favourable for the formation of filtering fistula in tissue which is relatively less vascular. Therefore, the Type II procedure is recommended and Type III for shallow anterior chambers. Type IV is reserved for special cases.

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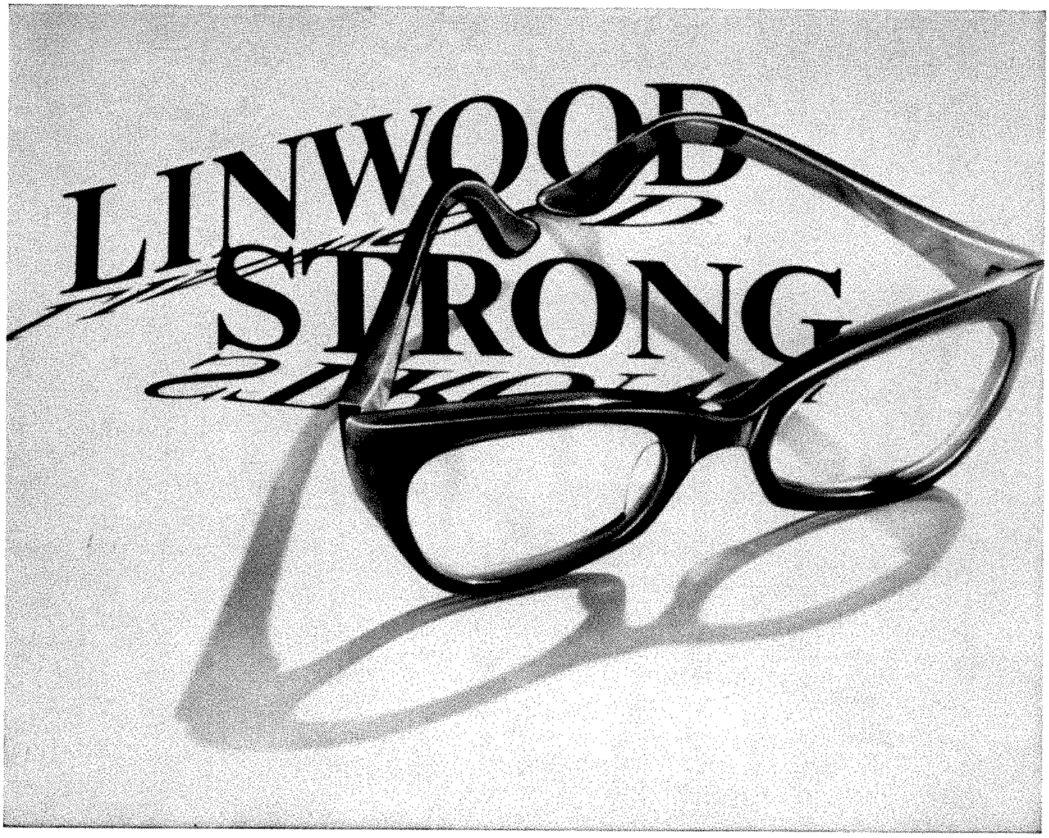

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Diazepam premedication in ophthalmic surgery

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Local anaesthesia offers many advantages to the surgeon working in a hospital where skilled anaesthetists and nurses are in short supply. Even where such facilities are adequate local anaesthesia avoids the almost inevitable delay between cases required by the administration of a general anaesthetic, and it may also be less dangerous to the frail or elderly patient.

The ideal ophthalmic anaesthetic should meet the following requirements:

(a) To provide the maximum tranquillizing effect without making the patient too drowsy to co-operate;

(b) To reduce extraocular muscle tone to keep the eye stationary during surgery;

(c) To lower intraocular pressure;

(d) To provide adequate analgesia;

(e) Not to cause vomiting;

(f) Not to affect blood pressure or respiration.

Diazepam (Valium), which meets most of the above requirements extremely well, is a tranquillizer of the benzodiazepine class, causing muscle relaxation and reduction of skeletal muscle tone (Randall, Heise, Schallek, Bagdon, Banziger, Boris, Mol, and Abrams, 1961). This action appears to be mediated through the central nervous system, for it can be shown that the stimulation of muscle through the motor nerve is unaffected. Animal experiments have shown that the respiratory centre and blood pressure are not affected (Parkes, 1967).

The pharmacological action of reducing the muscle tone is very advantageous in ophthalmic surgery, since reduction in extraocular muscle tone lowers the intraocular pressure (Colle, Duke-Elder, and Duke-Elder, 1931). Bruha (1964) measured the intraocular pressure in a series of patients before and after the administration of Diazepam, and in most cases in which the pressure was raised, there was a reduction to normal. Similar results were reported by Campan and Espagno (1966).

Present Investigations

Fifty unselected patients (26 men and 24 women) were operated upon for various ophthalmic conditions, using Diazepam 20 mg. intramuscularly one hour before operation as the sole premedication. Procaine hydrochloride (2 per cent.) was used for retrobulbar and facial nerve blocks.

The blood pressure was measured on admission and just before and after operation, and the respiration was observed during and after operation. Seven patients were emaciated and in a poor

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nutritional state. The operations carried out are shown in Table I, and the tribal and age groups in Table II. The tribal breakdown is important in Kenya as the nomadic tribes (Masai) are much less co-operative during surgery under local anaesthesia.

Table 1 *Operations performed in fifty cases*

Operation	*No. of cases*
Lens extraction	44
Glaucoma operation	4
Other	2
Total	50

Table II *Tribe and age groups of fifty patients*

Tribe	*Age group (yrs)*							*Total cases*
	30–39	40–49	50–59	60–69	70–79	80–89	90–100	
Kikuyu	1	4	4	15	6	–	–	30
Masai	–	2	–	2	2	–	–	6
Meru	1	–	–	–	–	–	–	1
Mkamba	1	1	–	4	1	–	2	9
Mluhya	1	–	–	–	1	–	–	2
Muhyau	–	–	1	–	–	–	–	1
Taveta	–	–	1	–	–	–	–	1
Total	4	7	6	21	10	0	2	50

Each patient's co-operative ability was noted before, during, and after operation. Any patient who persisted in bringing his hands up to his eyes or who did not lie still during the operation was termed 'unco-operative', as were those who would not lie still in bed or were mentally confused postoperatively.

Observations

Premedication with Diazepam was found to be highly satisfactory in the majority of cases, and there were no untoward side-effects.

BLOOD PRESSURE

This was unchanged in the majority, although a fall in systolic blood pressure of from 10 to 25 per cent. has been reported (Bruha, 1964).

RESPIRATION

This was unaffected and oxygen administration was not considered necessary.

CO-OPERATIVE ABILITY

This was satisfactory in 48 cases (Table III). Only two patients were unco-operative during surgery, both of them members of the nomadic Masai tribe. The problem was later successfully solved by supplementing the Diazepam with an intramuscular injection of 50 mg. pethidine one hour before the operation.

Table III *Co-operative ability*

Time	*Co-operative*	*Unco-operative*
Before operation	50	Nil
During operation	48	2 (both Masai)
After operation	50	Nil

A striking observation was that the patients who were given Diazepam alone were easily aroused and were fully co-operative and alert after surgery. This was a great advantage, as the need for post operative nursing care was minimal.

The majority of patients were able to get up out of bed the day after the operation. The muscular weakness reported by Bruha (1964) in some of his cases was not observed. Diazepam (20 mg.) was completely harmless in the poorly-nourished patients and in two patients over 90 years old. There was no nausea or vomiting and no vitreous loss.

Summary

(1) Fifty African patients undergoing intraocular surgery were given a single dose of 20 mg. Diazepam (Valium) one hour before operation, as the sole premedication.

(2) This was found to be highly satisfactory in all but two cases (4 per cent.). Excellent tranquillization was combined with good patient co-operation.

(3) The reduction in muscle tone and the associated fall in intraocular pressure provided by Diazepam premedication were considered to be valuable factors.

(4) The early ambulation and minimal nursing care required were of great advantage to both patients and hospital staff.

(5) Diazepam had no untoward effects on the poorly nourished or the very old.

I wish to thank Dr. G. G. Bisley, consultant ophthalmologist at the Kenyatta National Hospital, for his help and encouragement in writing this paper, the Director of Medical Services for permission to publish this paper, and Messrs. Roche Ltd. for supplying the Valium used in this trial.

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Brit. J. Ophthal. (1970) **54**, 276

Accessory extraocular muscle

T. H. KIRKHAM

Nuffield Laboratory of Ophthalmology, University of Oxford

The presence of an accessory extraocular muscle discovered at operation is reported for its intrinsic interest and to add to the literature on such anomalous muscular slips.

Case report

A 6-month-old baby boy was referred to the clinic because his parents had noticed a left convergent squint since birth. Pregnancy and birth had been normal. He was an only child and there was no family history of strabismus.

Examination

Although on cover test the child maintained fixation easily with either eye, he preferred to view with the right eye. A marked left convergent strabismus was present, the deviation being greater on accommodation; the cover test also showed alternating hypertropia. When fixing with the right eye the horizontal deviation was approximately 35^{Δ} with left hypertropia and when fixing with the left eye it was 40^{Δ} with right hypertropia. Both eyes showed a gross symmetrical elevation in adduction although there was no V phenomenon. Atropine refraction revealed a low degree of hypermetropia. The fundi were normal.

Alternation was achieved and maintained after a 3-month period of conventional part-time right occlusion. Surgery was planned when the child was 17 months old to reduce the horizontal deviation and the unsightly elevation in adduction.

Operative findings

Forced duction tests revealed no undue resistance in any direction.

The left medial rectus was recessed 4 mm. and the left inferior oblique was anteroposed to 3 mm. from the lateral rectus insertion and recessed to 6 mm. below the lateral rectus border.

The right medial rectus was recessed 4 mm. When the right inferior oblique was exposed, it was found to be a much thinner muscle than the left inferior oblique, but otherwise it appeared healthy; its insertion was left undisturbed.

In the course of dissection of the right inferior oblique muscle, an abnormal muscular slip was discovered lying between the lateral and inferior rectus muscles. The insertion of this accessory muscle was 5 mm. broad and it was attached to the globe 7·2 mm. from the limbus and 4 mm. lateral to the inferior rectus insertion. The slip was resected at its insertion and explored as far as the crossing of the inferior oblique and inferior rectus muscles, from which point it appeared to arise. The lateral and inferior rectus muscles appeared normal, healthy muscles.

Result

Postoperatively there was an esotropia of 15^{Δ} and some symmetrical elevation on adduction remained.

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Comment

Scobee (1948), in discussing abnormal check ligaments, abnormal muscle slips, and abnormal muscle insertions, felt that 90 per cent. of cases of heterotropia appearing in the first 6 years of life had some underlying anatomical cause for the deviation. This comment is surprising in view of the extremely sparse literature concerning accessory muscles or abnormal muscular slips, which was well summarized by Fink (1958).

The accessory muscle in the present case was considered to be an additional insertion of the right inferior oblique, since the latter muscle was much thinner than on the left. From its position this muscle might have been expected to act as a depressor and extortor of the globe; its presence was totally unexpected from preoperative examination of the ocular movements.

An accessory inferior oblique muscle arising from the inferior oblique passing to the common tendinous origin and into the optic nerve sheath was described by Posey (1923). A similar abnormal muscular bundle (Rex, *quoted by* Whitnall, 1921) passing from the orbital apex to join the inferior oblique and inferior rectus supplied by the third nerve was present in both orbits. There is no report of an abnormal muscle slip similar to the one described in the present case.

I am indebted to Mr. Arnold Freedman for permission to report this case.

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Brit. J. Ophthal. (1970) **54,** 278

Oculo-cerebro-renal syndrome

Report of a case in a baby girl

L. S. HARRIS, K. A. GITTER, M. A. GALIN, AND
G. P. PLECHATY

From the Department of Ophthalmology of the New York Medical College

The oculo-cerebro-renal syndrome of Lowe is characterized by failure to thrive, mental retardation, hypotonia, cataracts, glaucoma, amino-aciduria, and decreased renal ammonia formation (Lowe, Terrey, and MacLachlan, 1952). A single report of a female with these findings exists in the literature (Švorc, Masopust, Komárková, Macek, and Hyánek, 1967). In all other characteristic cases, the genetic pattern has been consistent with an X-linked recessive mode of inheritance. Consequently, only males have been afflicted with this condition (Chutorian and Rowland, 1966; Schwartz, Hall, and Gabuzda, 1964; Švorc and others, 1967). Moreover, to the best of our knowledge, no case has been reported in a Negro subject.

We have had the opportunity to study a Negro female child with clinical and laboratory findings consistent with the diagnosis of Lowe's syndrome. The current report is concerned with these findings and a discussion of the implication.

Case report

A 10-day-old female infant was first admitted to the Flower and Fifth Avenue Hospitals Division of the New York Medical College with bilateral cataracts and megalocornea. The family history and pregnancy were entirely unremarkable. The general physical examination disclosed only ocular abnormalities which consisted of enlarged oedematous corneae. Examination under general anaesthesia revealed the corneal diameters of both eyes to be 11 mm. Posterior synechiae were noted in both eyes and scale readings with the Schiøtz tonometer with the 7·5 g. weight were recorded as 4·5 and 7·5 mm. Hg on the right and left respectively. Laboratory studies disclosed 3+ proteinuria and generalized amino-aciduria. Blood amino acid levels were normal.

Chromosome studies revealed a normal female karyotype. A bone marrow biopsy was negative for cystine crystals. Urine tests for cytomegalic inclusion disease and blood tests for rubella antibodies both gave negative results. Investigations for toxoplasmosis and mucopolysaccharidosis also gave negative results.

The patient was again admitted to hospital 5 months later, when she was noted to be small, underdeveloped, hypotonic, and hypoactive (Figure), having gained only 6 lb. in the first 8 months of life. The ocular findings at this time were unchanged, but mild hepatosplenomegaly and motor and mental retardation were observed. Urine was negative for galactose but showed generalized amino-aciduria and revealed the presence of proline and hydroxyproline. A bone survey at this time showed no evidence of rickets. An ammonium loading test was performed and showed normal renal production of ammonia in response to an induced metabolic acidosis. Examination under general anaesthesia revealed corneal diameters of 12·5 and 13 mm. on the right and left respectively. Schiøtz tonometer readings with 7·5 g. weight were 3·0 and 3·5 mm. Hg on the right and left respectively. A direct goniotomy was performed at this time on the right eye.

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Address for reprints: Dr. L S. Harris, M.D., Department of Ophthalmology, New York Medical College, 1249 Fifth Avenue, New York, N.Y. 10029, U.S.A.

FIGURE *A 6-month-old female child with the oculo-cerebro-renal syndrome*

A follow-up in the ensuing 11 months has shown this child to be hyporeflexic, mentally retarded, and in the lower 3 percentile in growth and development. She has had frequent intercurrent infections which have responded to antibiotics.

More recent examination under anaesthesia showed the corneal diameter to be 12·5 and 13 mm. on the right and left respectively. Schiøtz readings with the 7·5 g. weight were 3·0 and 4·0 mm. Hg on the right and left respectively. A-scan ultrasonography disclosed axial lengths of 24 mm. bilaterally. Lens diameters were 2 mm. bilaterally.

Ocular examination of the mother and female siblings failed to disclose punctate lenticular opacities or any other ocular abnormality.

Discussion

Lowe and others (1952) first described three unrelated males with glaucoma, cataracts, mental retardation, and hypotonia. All were acidotic and had amino-aciduria with decreased renal ammonia production in response to an induced metabolic acidosis. The pattern of inheritance indicated an X-linked recessive mode of transmission and therefore only males were affected clinically (Chutorian and Rowland, 1966; Schwartz and others, 1964; Wilson, Richards, and Donnell, 1963).

Ocular pathological changes in Lowe's syndrome may be so specific as to be virtually diagnostic. The important findings in this regard are exceedingly thin cataractous crystalline lenses (Curtin, Joyce, and Ballin, 1967). Ultrasonography in the present case confirmed the presence of buphthalmos, but more significantly, demonstrated the presence of small thin lenses. This finding in a child with glaucoma, hypotonia, mental retardation, and amino-aciduria is certainly suggestive of the syndrome described by Lowe.

Several objections might be raised to the inclusion of this patient in the category of Lowe's syndrome. Foremost amongst these is the fact that the mode of inheritance is believed to correspond to an X-linked recessive pattern. If this is correct, only males will be affected with the clinical syndrome. Švorc and others (1967) have, however, reported a proven female with cataracts, mental and motor retardation, hypotonia, and amino-aciduria. As in the present case the relatives showed no abnormality.

As with a number of other heritable states, the female carrier has been shown to possess certain subclinical findings. More prominent amongst these are non-progressive punctate lenticular opacities which do not impair visual acuity. Amino-aciduria induced by orinthine loading has also been documented in female carriers of this condition (Chutorian and Rowland, 1966; Schwartz and others, 1964).

The patient reported here is unequivocally female on the basis of chromosome studies. It is of interest to note, however, that a significantly high incidence of cryptorchidism occurs in Lowe's syndrome. In one series, this approached an incidence of 80 per cent. (Chutorian and Rowland, 1966). Despite this observation, chromosome studies have not been routinely reported and it is therefore possible that a few misdiagnosed females have been included in the literature.

Bilateral posterior synechiae were noted in the present case. Although this finding has not been previously noted, not all patients reported in the literature have been subjected to biomicroscopy, so that it could have been overlooked. Moreover, in the histological study of this entity by Curtin and others (1967), the anterior chamber was filled with proteinaceous material. Clinically, this finding has been felt to be a prerequisite for synechia formation.

Initially, Schwartz and others (1964) reported derangements in ornithine metabolism as a prime defect in this condition. This finding was confirmed by Sidbury and McCarty (1963). However, later studies in patients with similar clinical findings have failed to confirm this specific pattern of amino-aciduria. Moreover, recent reports have shown that the pattern of amino-aciduria in a given patient is highly variable, both during the course of any one day and from day to day. In fact, in patients with amino-aciduria from any cause, the urinary excretion of amino acids depends on the dietary intake of protein (Chutorian and Rowland, 1966; Worthen and Good, 1958). Certainly, then, amino-aciduria is a *sine qua non* of the oculo-cerebro-renal syndrome, but the specific pattern of excretion requires further elucidation.

The patient here reported had no demonstrable defect in renal ammonia production when challenged with an induced metabolic acidosis. The three related children reported by Schwartz and others (1964) did not have this defect either, but they were felt to be representative of Lowe's syndrome.

Certainly, the basic metabolic and biochemical defects in Lowe's syndrome are not known, and it is thus impossible to define the condition precisely. Our patient has the clinical manifestations of an oculo-cerebro-renal syndrome, and as in those presented by Schwartz and others (1964), there is no defect in ammonia production. The spectrum of the oculo-cerebro-renal syndrome encompasses a number of different biochemical defects, and until these can be precisely determined, it may be well to group all such patients under this general heading.

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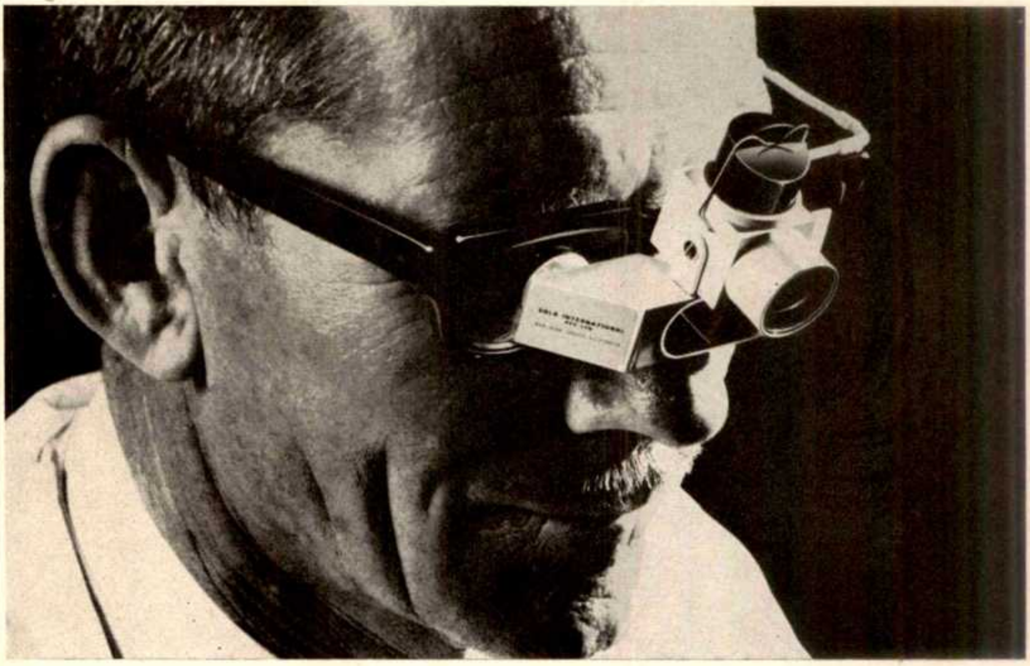

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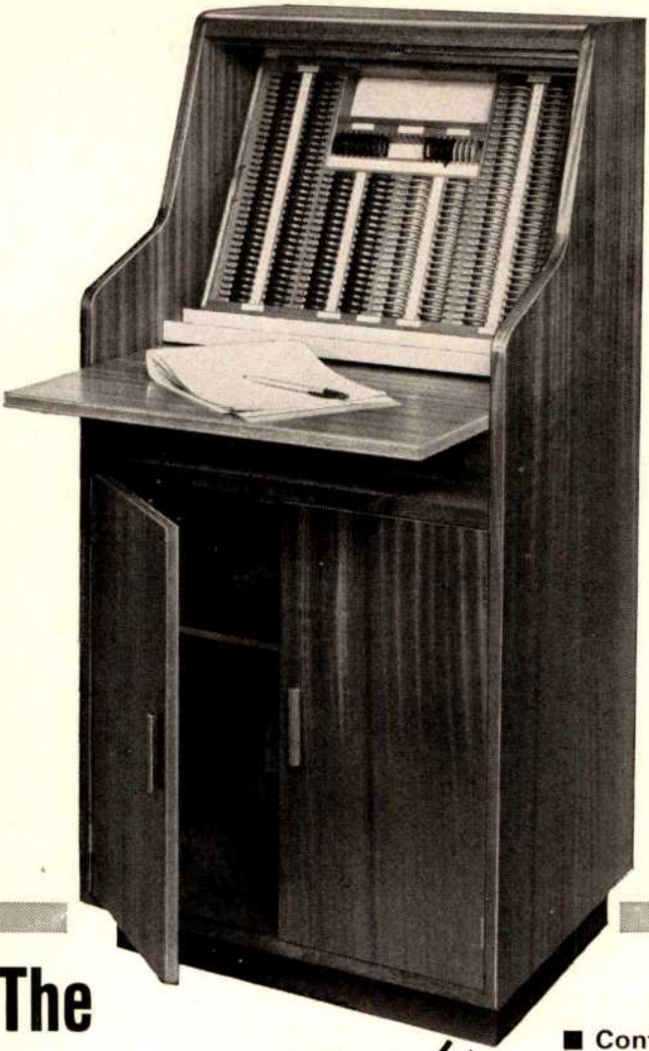

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Brit. J. Ophthal. (1970) **54**, 281

Squamous cell carcinoma of the oesophagus with choroidal metastasis

JOAN MULLANEY

National Ophthalmic Pathology Laboratory and Registry of Ireland, Royal Victoria Eye and Ear Hospital, Dublin

The occurrence of carcinoma metastasizing to the intraocular tissues is unusual but the world literature contains reviews of large series of cases. The sites of the primary growths have been extensively documented, with the breast and lung being the commonest sources. Examination of the available literature appeared to suggest the existence of only one previous description of carcinoma in the eye secondary to an oesophageal primary growth, a surprising rarity in view of the thoracic situation of the oesophagus. Larsen (1933) described a secondary deposit in the right iris in a patient initially seen with a squamous cell carcinoma of the lower third of the oesophagus diagnosed by oesophagoscopy. Death took place 2 months after the first presentation. A squamous cell carcinoma was confirmed in autopsy iris tissue. The choroid was clinically free of tumour.

This paper describes what appears to be the first reported case of carcinoma of the oesophagus metastasizing to the choroid.

Case report

A 67-year-old man presented with a 6 months' history of dysphagia and considerable weight loss. A barium swallow showed a carcinomatous stricture in the middle third of the oesophagus (Fig. 1).

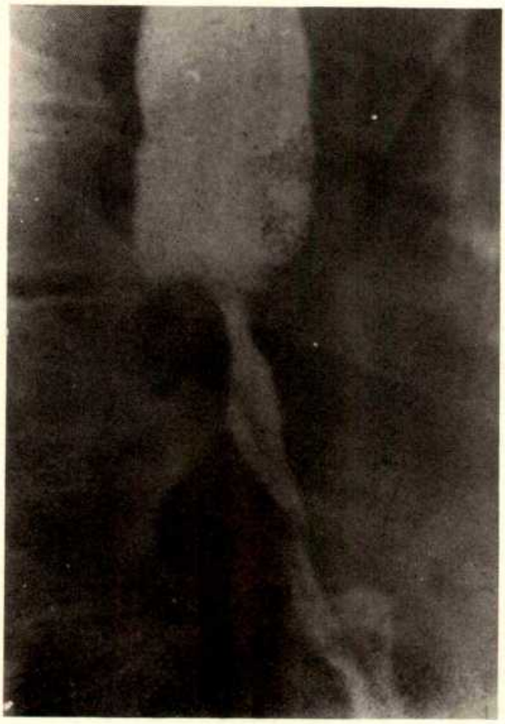

FIG. 1 *Oblique view of barium-filled oesophagus showing stricture*

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His general condition was too poor for a thoraco-abdominal operation. Laparotomy to insert a Bardon tube was unsuccessful because of the degree of stricture and a feeding gastrostomy was performed.

There was no clinical or radiological evidence of metastases at this time, but 6 months later he complained of pain in the right eye.

Examination

There was absence of transillumination, a shallow solid retinal detachment, and secondary glaucoma. Metastatic oesophageal cancer of the choroid was diagnosed and enucleation was performed.

Result

In spite of his low state of health the patient survived a further 6 months, and died a year after the laparotomy.

GROSS PATHOLOGY

The specimen consisted of a right eye measuring 24 × 24 × 23 mm. with no external abnormality. Examination of the opened specimen (Fig. 2) showed massive infiltration of the superior temporal choroid by yellowish convoluted tumour tissue which extended into the ciliary processes. There was an associated flat retinal detachment.

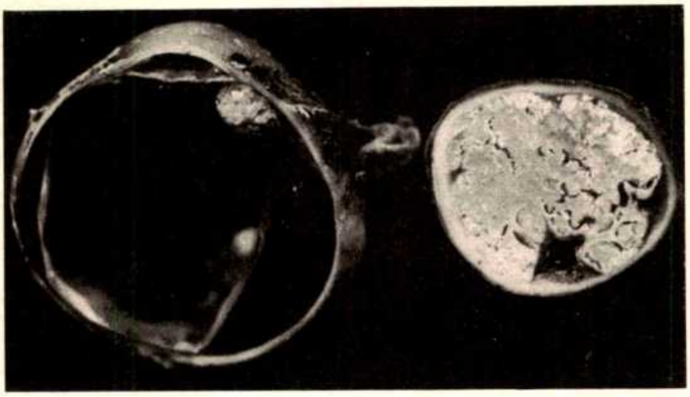

FIG. 2 *Choroidal and ciliary body tumour infiltration in opened globe*

HISTOLOGY

The main finding at microscopy was the presence of a well-differentiated keratinizing squamous cell carcinoma (Fig. 3) filling the choroid and extending at some levels to involve the posterior portion of the ciliary body. No scleral or extraocular infiltration was seen. The uveal tract contained scattered reactive chronic inflammatory cells. The iris and filtration angles appeared within normal limits and the optic disc and nerve were not morphologically abnormal. The retina showed secondary degenerative changes and the detached areas had underlying fluid accumulation.

Summary

Carcinoma of the oesophagus metastasizing to the eye appears to be extremely rare. This paper describes what appears to be the first reported case of such an occurrence in the choroid.

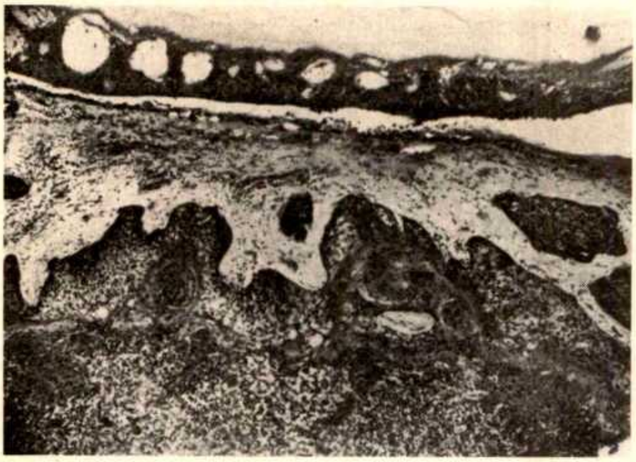

FIG. 3 *Keratinizing squamous cell carcinoma in the choroid, showing degenerate peripheral retina at top. Haematoxylin and eosin.* × 100

I wish to thank Mr. Harris Tomkin, ophthalmic surgeon, for permission to report this case, Mr. J. S. R. Lavelle, F.R.C.S.I., for clinical and surgical information, and Mr. R. J. Lester, F.I.M.L.T., for technical assistance.

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Brit. J. Ophthal. (1970) **54,** 284

Astrocytoma of the optic nerve

HARI MOHAN AND D. K. SEN

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Though two-thirds of the primary optic nerve tumours that have been reported are astrocytomata (Davis, 1940), these tumours are of rare occurrence. In the course of 15 years, Collins and Marshall (1900) found only two cases of astrocytoma of the optic nerve among 388,000 patients. The astrocytoma present in the optic nerve belongs to the least malignant type of glioma, Grade I, which is usually found in young children (Hudson, 1912; Reese, 1963). It usually manifests itself as a very slowly progressive unilateral proptosis with no pain or ocular change except poor vision occasioned by optic atrophy (Reese, 1963). It advances by direct extension along the intraneural portion of the nerve and does not penetrate the sheath, so that a diffuse and uniform hyperplastic swelling is produced (Duke-Elder, 1940). Recurrences are very rare in intraorbital cases after successful excision.

As the case reported here has some very unusual features, we thought it worthwhile to put these on record.

Case report

A 45-year-old male Hindu reported to the eye out-patient department of Irwin Hospital with the complaint of gradual protrusion of the left eyeball for 6 months with pain for the last 2 months. He had been hit on the forehead just above the left eye by a bamboo pole 7 months previously.

Examination

RIGHT EYE: Normal in all respects. Visual acuity 6/6.

LEFT EYE: Eyeball displaced forwards, downwards, and outwards (Fig. 1). No mass felt in the orbit. No perception of light. Ocular movements restricted in all directions. Both lids swollen. Conjunctiva chemosed and congested. Pupil dilated and fixed. Optic disc markedly atrophic. Exophthalmometric reading (Hertel) 26 mm. (normal right eye 15 mm.).

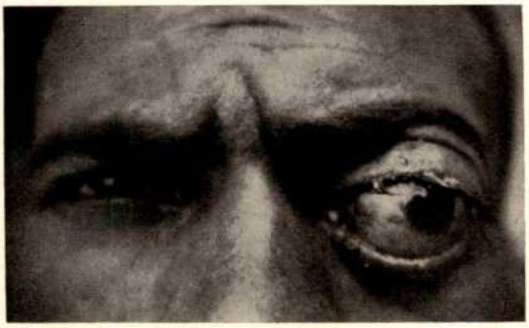

FIG. 1 *Displacement of left eyeball forwards, downwards, and outwards*

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Systemic examination, including complete neurological examination, revealed nothing abnormal. Thyroid and blood studies and serological tests for syphilis negative. Frontal and maxillary sinuses normal on transillumination. Skiagrams of skull, paranasal sinuses, orbits, and optic foramina normal.

Surgery

As all the signs pointed to a rapidly-growing intraorbital space-occupying lesion, the orbit was opened up by Kronlein's procedure. The tumour was found to extend anteriorly right up to the attachment of the optic nerve to the globe but posteriorly it did not involve the canalicular portion of the optic nerve. It was, therefore, decided to sacrifice the eye together with the tumour, and the globe was excised with the optic nerve up to the apex of the orbit (Fig. 2).

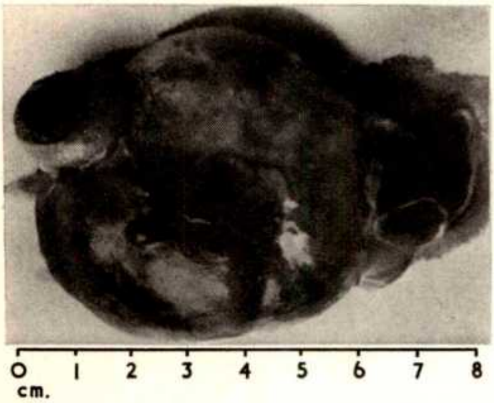

FIG. 2 *Excised specimen, showing eyeball and tumour*

Result

Postoperative recovery was uneventful. Histopathological examination identified the tumour mass as an astrocytoma Grade II (Fig. 3).

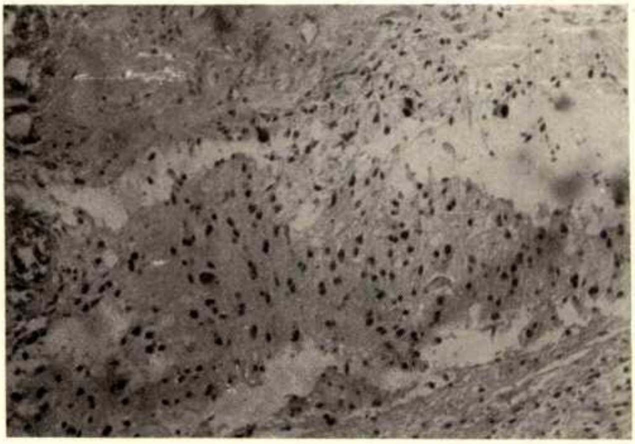

FIG. 3 *Section of tumour, showing astrocytoma Grade II. Haematoxylin and eosin.* × 100

Comment

This type of tumour is very uncommon at the age recorded here. The most common site of origin is the region of the optic foramen from which extension occurs in both directions, so that enlargement of the optic foramen is important in diagnosis. In this case the tumour arose from the intraorbital portion of the optic nerve.

The growth and development of the tumour is usually slow with no pain in the eye, but in this case the tumour grew fairly rapidly, and pain was probably due to stretching of the nerve sheath. This rapid growth probably caused other unusual features, such as swelling of the lids and chemosis and congestion of the conjunctiva. The blow sustained by the patient may have been responsible for this unusual development.

Summary

A case of astrocytoma (Grade II) arising from the intraorbital portion of the optic nerve at the age of 45 is recorded. The unusually rapid progress of the tumour may have been due to a blow on the forehead just above the affected eye.

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Brit. J. Ophthal. (1970) **54**, 287

Book reviews

System of Ophthalmology. Vol. XI. Diseases of the Lens and Vitreous; Glaucoma and Hypotony. Edited by S. DUKE-ELDER. 1969. Pp. 779, 686 figs, 9 col. pl., bibl. Kimpton, London. (£11.)

Volume XI of the *System of Ophthalmology* presents three separate sections. The first concerns itself with diseases of the lens and particularly with cataract: its aetiology, pathology, symptomatology, clinical types, and treatment. Although there have been marked advances in the surgical management of cataract over the last 30 years, its aetiology remains a complicated enigma which defies even the pen of Duke-Elder.

Diseases of the vitreous comprise the second section. They are largely degenerative in nature but may lead to changes in the retina which endow them with vital importance.

The third section is devoted to glaucoma and hypotony. There is a masterly description of the primary glaucomas which makes them sound easier to manage than they often are in practice. Secondary glaucoma has a chapter on its own and herein are described the many examples of glaucoma arising in association with systemic disease. A final short chapter on hypotony completes a volume of 779 pages.

As in all Duke-Elder's productions the facts are allowed to speak for themselves but they are so marshalled and arrayed that the ensemble acquires a dynamism greater than the sum of its components, a dynamism which suspends disbelief or criticism. The content is, as always, scientifically accurate; the form inimitable. Who can compete with such monumental industry?

Problems of Industrial Ophthalmology. 1st and 2nd Symposia of the International Study Group for Ergo-ophthalmology: Munich 1966 and Amsterdam 1968. Edited by H.-J. MERTÉ. 1969. Pp. 288, 79 figs. Karger, Basel. (148*s.*)

This book about occupational ophthalmology contains 57 papers, read at Munich in 1966 and at Amsterdam in 1968, dealing with the relations of the visual capacity of the worker and the efficiency of his work, industrial hazards and ocular injuries, illumination of the place of work, and the psychological factors involved in partial sight and in blindness. It is unavoidable that there should be some overlapping of the subjects. Many statements are generally known, *e.g.* it is accepted that the personality of a motorist is more important than perfect visual acuity and binocularity. The investigations of Dubois-Poulsen on motor and sensory visual fatigue, which may involve the extra-ocular muscles, the ciliary muscle, the retina, and the higher cerebral centres, are very interesting. Schober discusses functional myopia, which can occur when using optical instruments. Krejči reports good results of irrigating the eye with DETA (di-ethylon-triamine) in cases of caustic injury caused by formaldehyde, phenol, and acids. In severe injuries, however, preliminary perilimbal (Passow) opening of the chemotic conjunctiva must be performed. Jacobi and Rüther have carried out experiments in rabbits on lens changes caused by 15-MeV neutrons and the inhibitive value of intraperitoneal injections of compounds containing serotonin.

Among the many attractive papers none is devoted to the psychological and ocular requirements of the ophthalmic surgeon. Evidently, a perfect von Graefe section requires good visual acuity, binocular depth appreciation, and a well-trained kinaesthetic sensation of the hand and fingers. The psychological factor is difficult to determine. Intuition is important for its evaluation. Binocularity is also required for slit-lamp examinations. The optical equipment of the ophthalmic "worker" should be worthy of consideration in future international study groups.

Notes

Barraquer Gold Medal

The Gold Medal Communalis Ignacio Barraquer y Barraquer has been awarded to Professor Tadeusz Krwawicz of Lublin, Poland, for his introduction and development of the technique of cryoextraction. The presentation is to be made by the President of the Republic of Colombia in Bogotá on March 16, 1970.

V Seminar on Clinical Echo-ophthalmography

Vienna, May 11 to 15, 1970

The V Vienna Seminar on Clinical Echo-ophthalmography (training programme for beginners and advanced students) will be held on May 11 to 15, 1970, at the IInd Ophthalmology Service (Head: Prof. J. Boeck), University of Vienna Medical School.

For further information and registration please write to: Dr. Karl Ossoinig, c/o II Ophthalmology Service, University of Vienna Medical School, Alserstrasse 4, 1090 Vienna, Austria.

Obituary

Campbell Shaw, 1896–1969

Campbell Shaw, formerly senior ophthalmologist at Bournemouth, died in December at the age of 73. He was born and educated in Wales and during the first world war he served as a surgeon probationer in the R.N.V.R., before returning to St. Bartholomew's Hospital on demobilization to qualify in 1920.

His first house appointment was as house physician to Dr. Drysdale, and he later joined the Eye Department of St. Bartholomew's Hospital under Holmes Spicer and later Foster Moore, for whom he always retained the greatest respect and affection.

For several years he was in general practice at Basingstoke, but continuing as clinical assistant to the Eye Departments of Barts and Moorfields. In 1935, he was appointed ophthalmic surgeon to the Royal Victoria Hospital, Bournemouth, and eventually retired from hospital practice in 1961. He was a founder member of the Southern Ophthalmological Society in 1945, his worth being soon recognized when he was elected President in 1951.

As a young man, he was a sportsman of renown. A formidable rugby forward, he captained Barts when they were in the final of the Hospital Cup in 1920, and he also played for the Barbarians. Sailing on the Broads and at Poole, and stamp collecting, were two of his hobbies and he found great relaxation in his garden.

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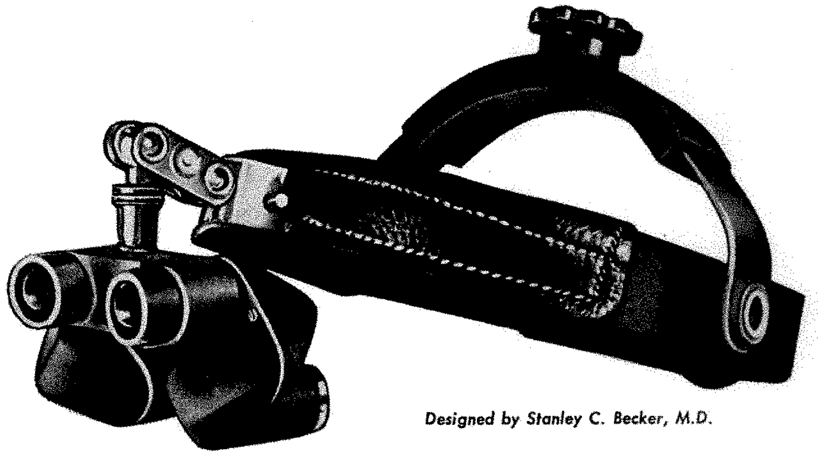

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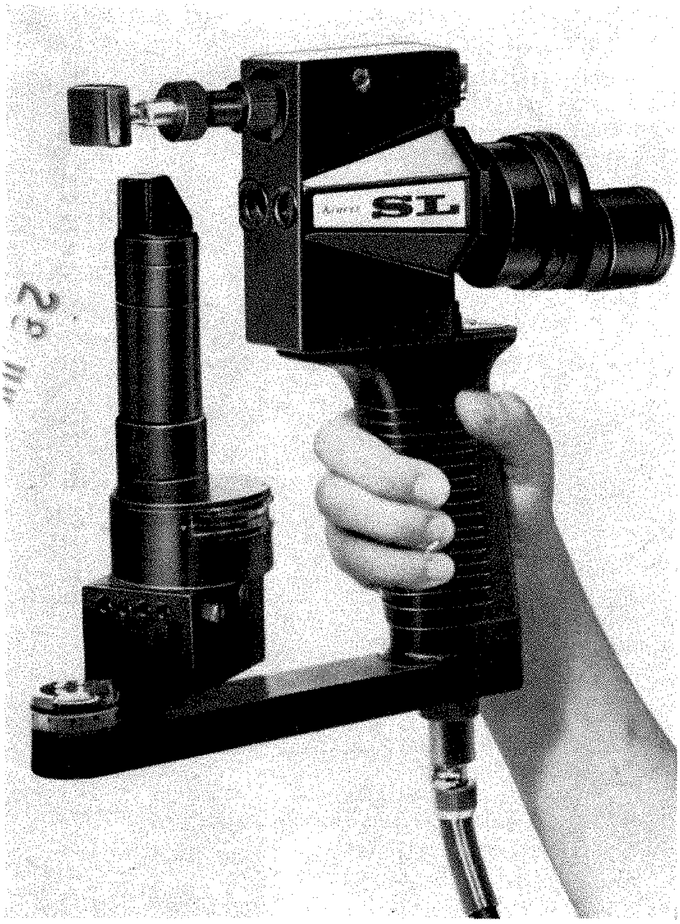

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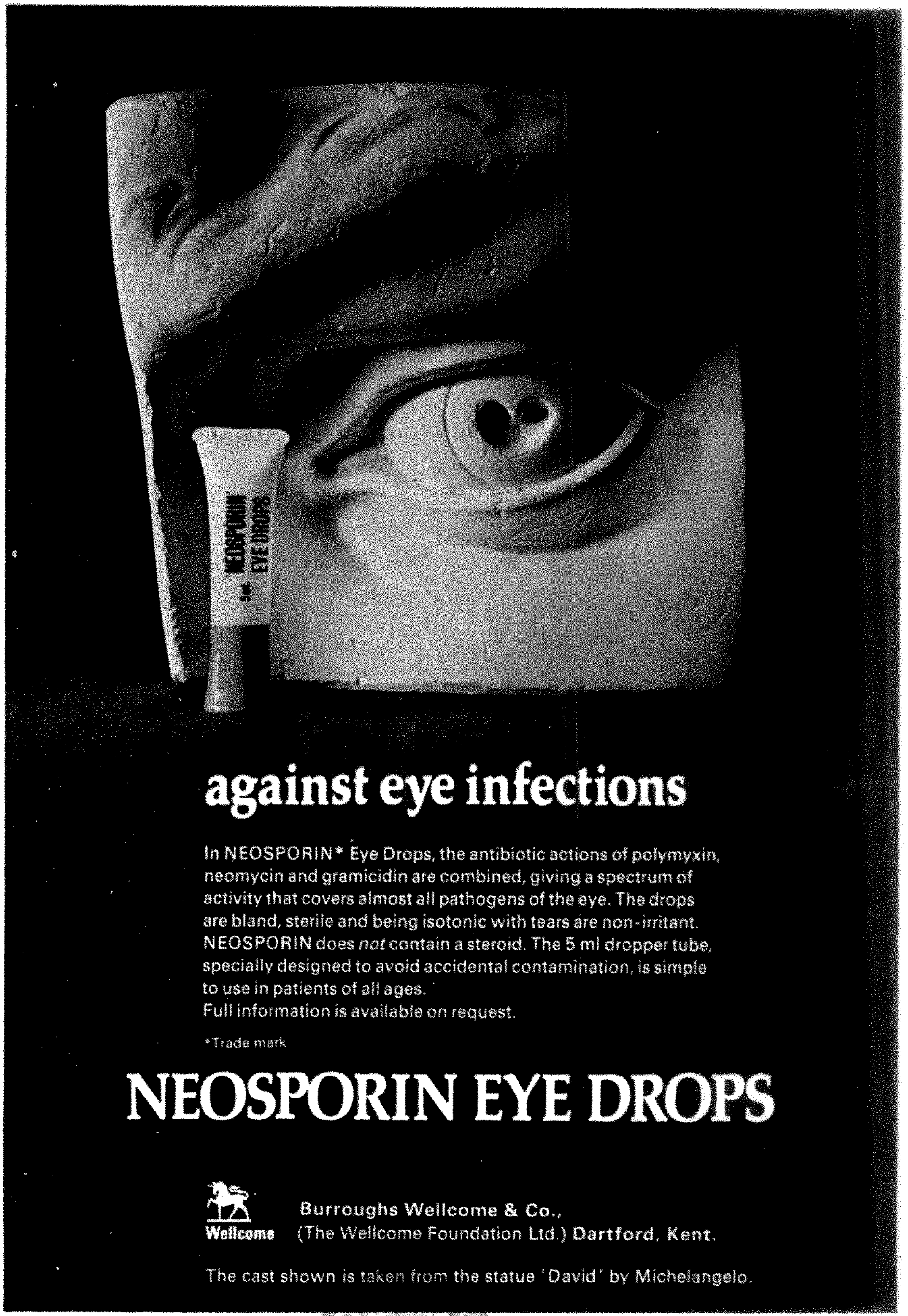

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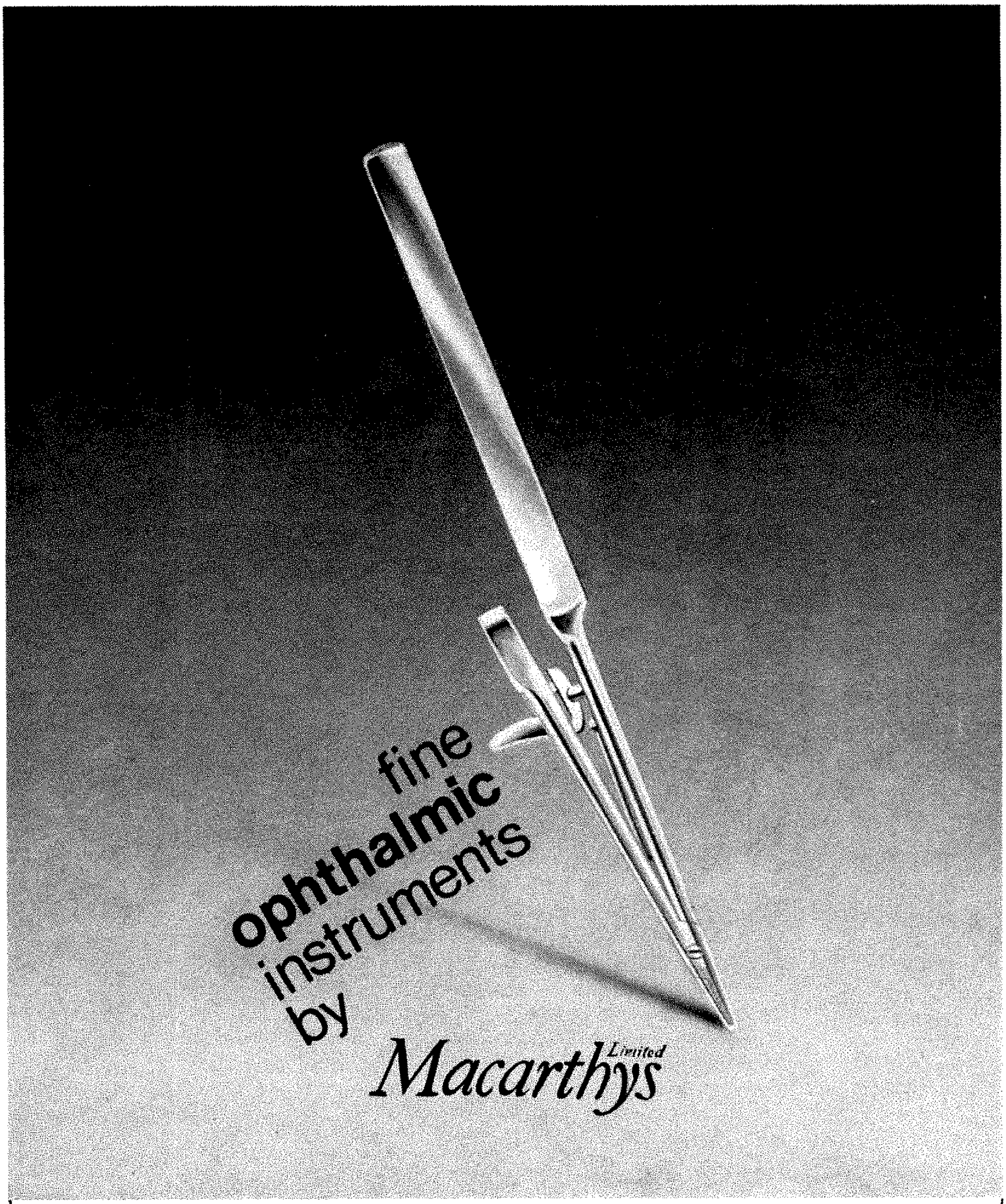

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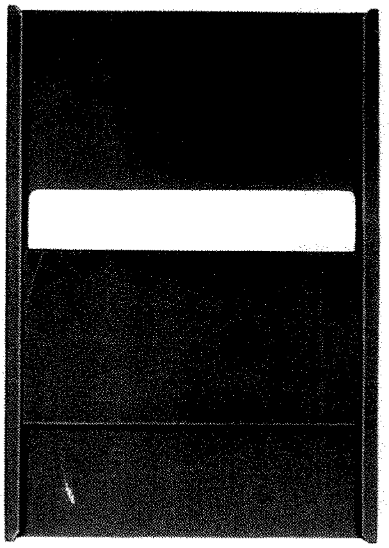

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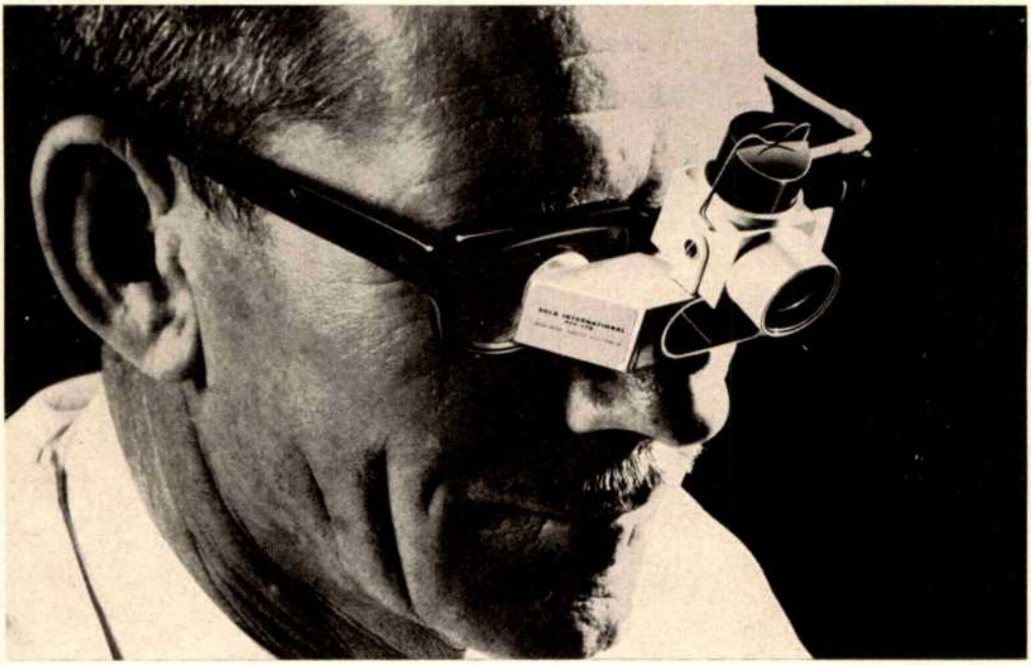

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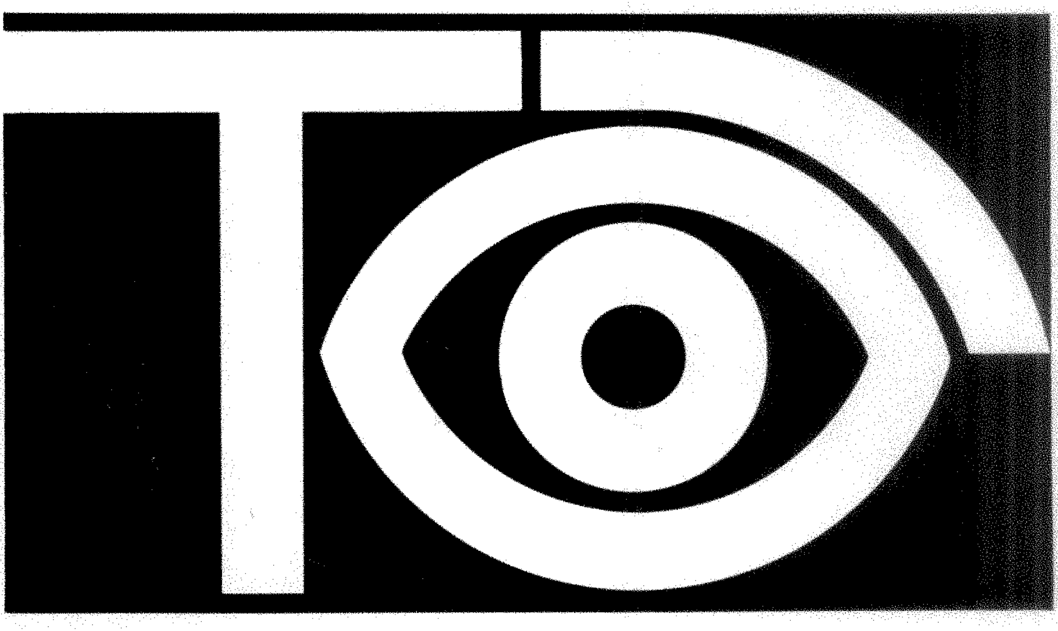

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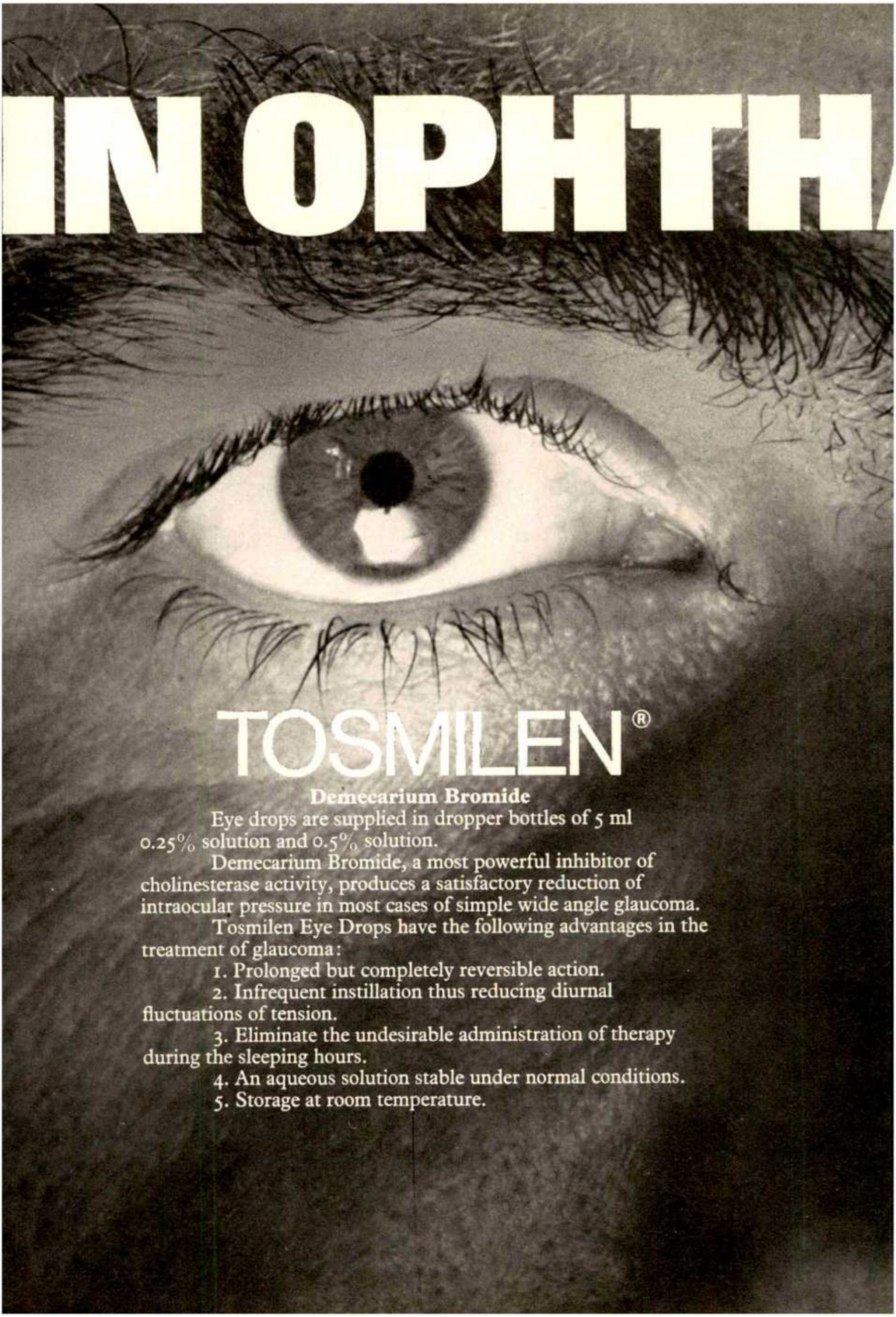

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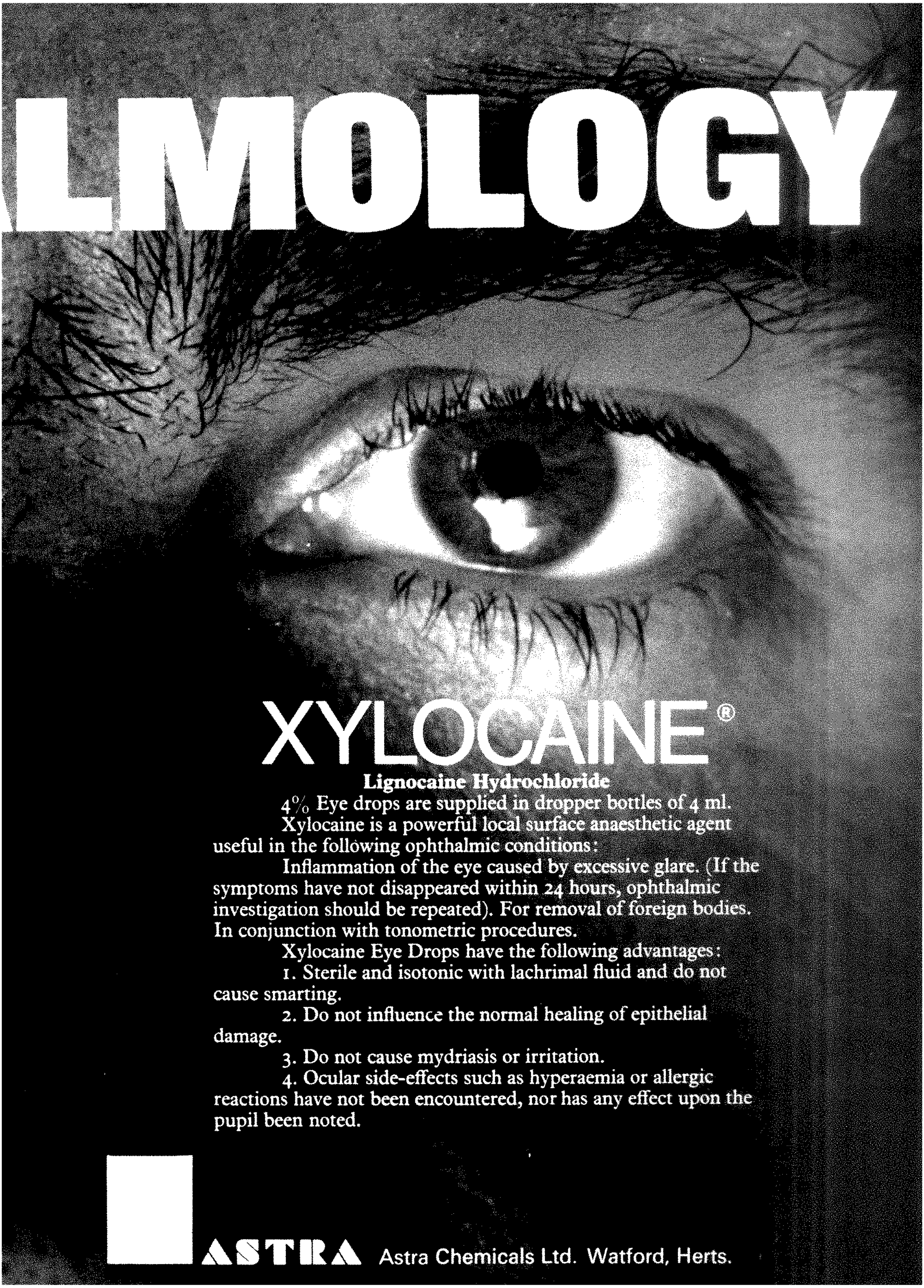

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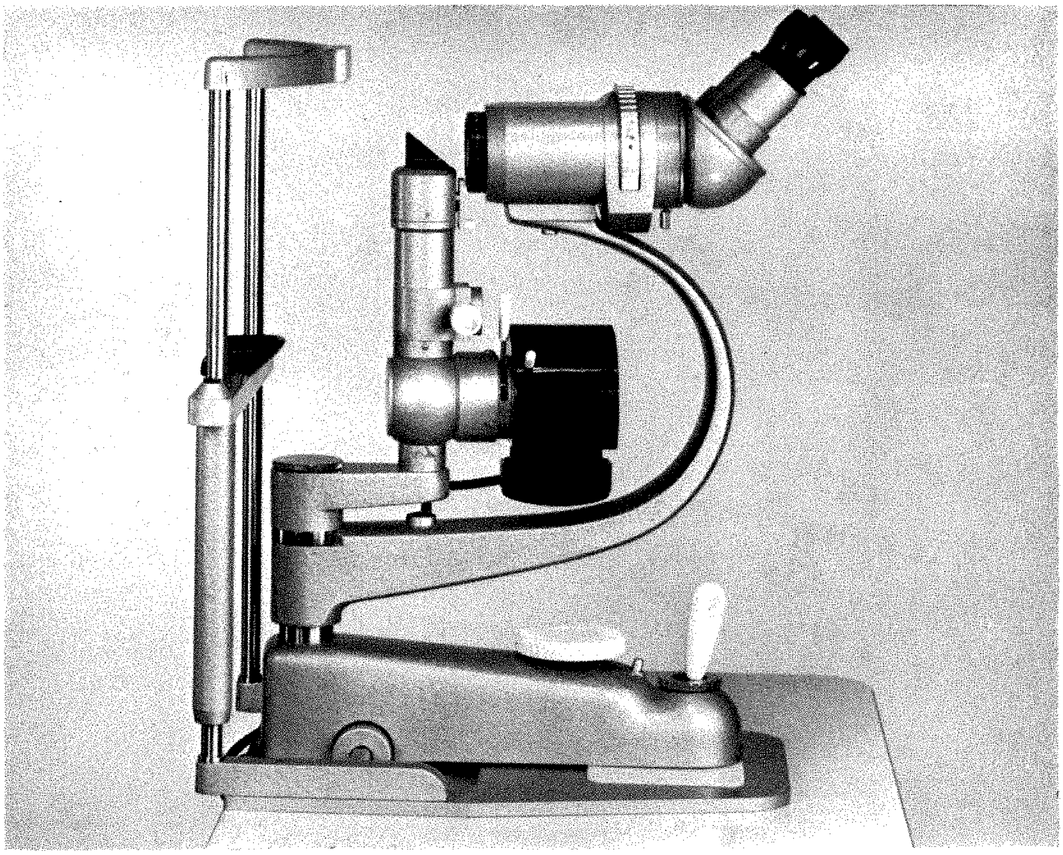

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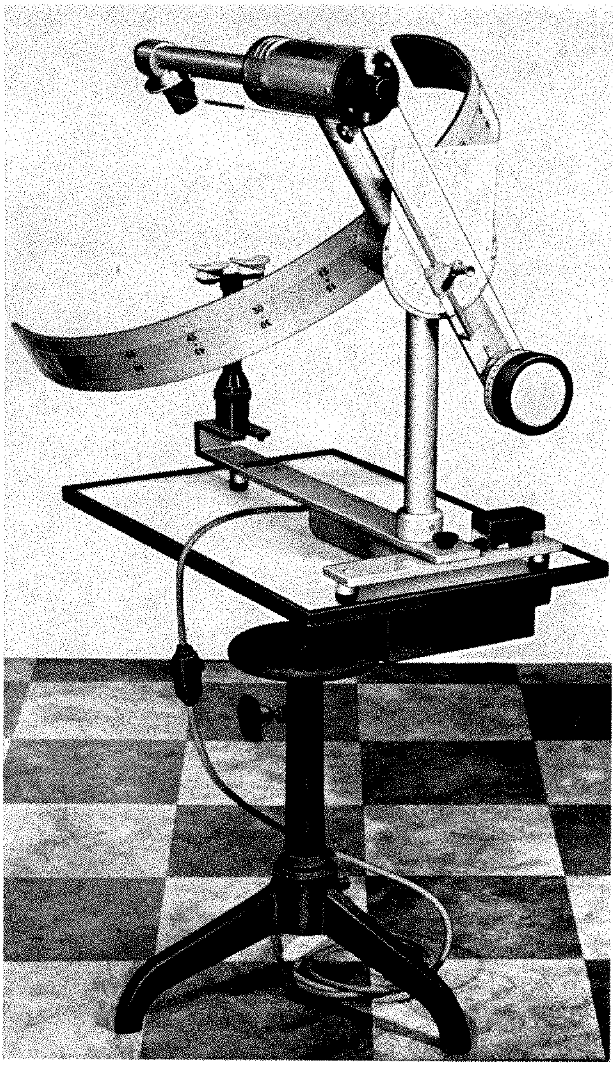

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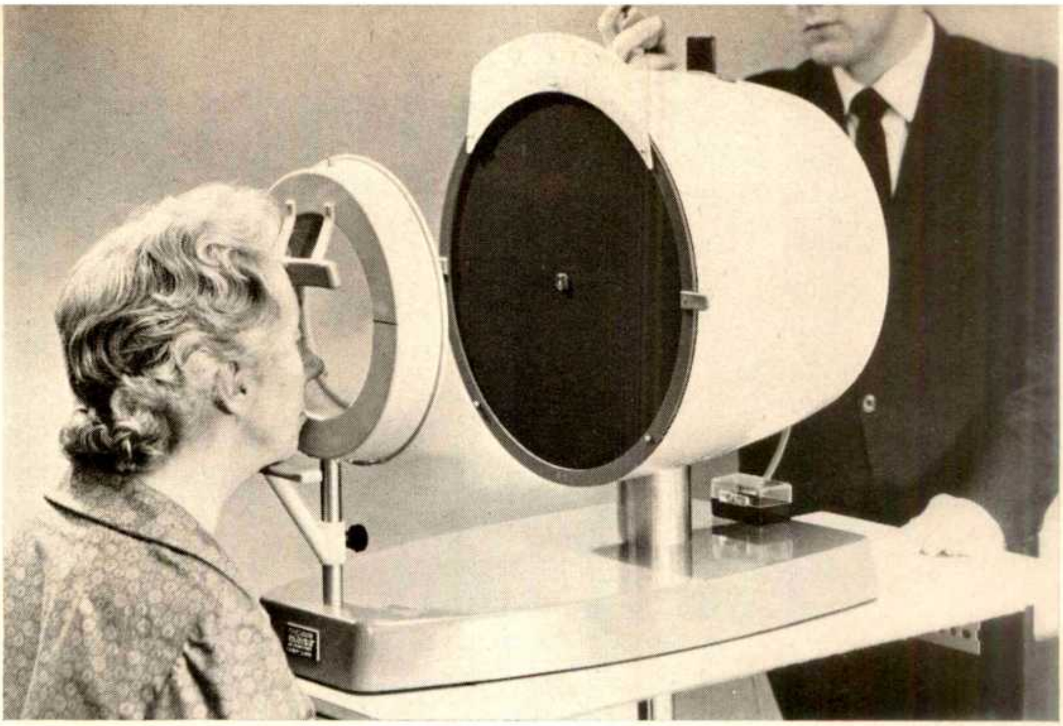

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Serial Analysis of changes in visual field defects, employing a new instrument to determine the activity of diseases involving the visual pathways. Ophthalmologica (Basle) 152.1. (1967).

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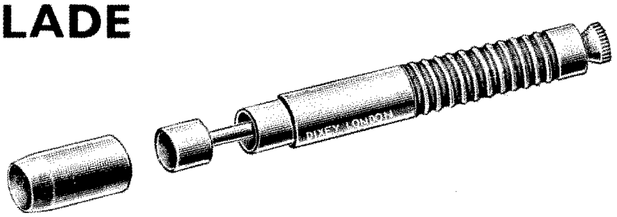

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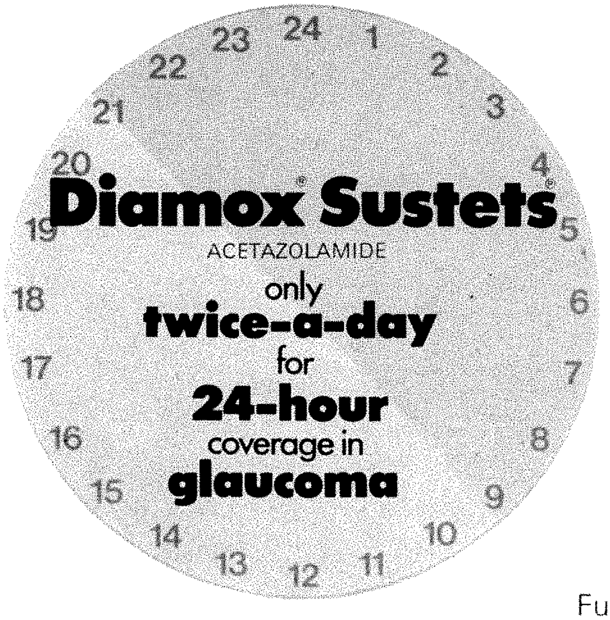

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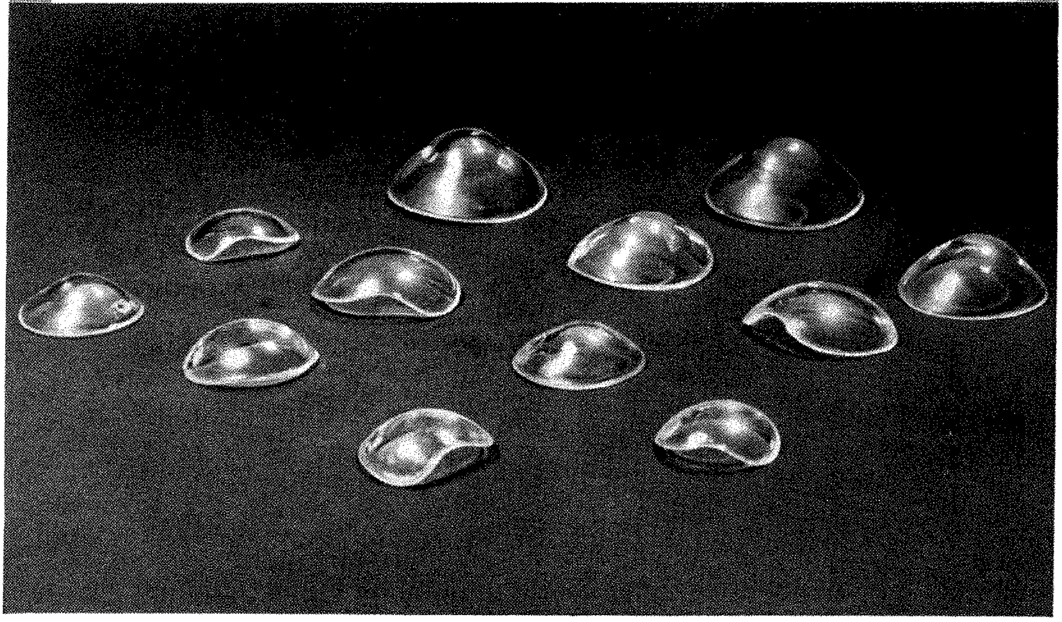

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Communications

Pathogenesis of visual field defects

Role of the ciliary circulation

SOHAN SINGH HAYREH
Institute of Ophthalmology, University of London

Clinically the presence of nerve fibre bundle defects in glaucoma and non-glaucomatous lesions, and altitudinal or vertical hemianopias in pre-chiasmal lesions has been known for a long time. These suggest a sectoral lesion in the optic nerve or retina. In the majority of such cases, no retinal lesion is seen to account for these visual field defects. It has been presumed that the lesion lies in the optic nerve. Such a visual field defect can be produced only by a sectoral lesion. Most of these field defects are considered to be vascular in origin, but studies of the blood supply of the optic nerve have so far failed to demonstrate any segmental blood supply to the nerve which could explain them. The present study demonstrates such a sectoral blood supply in the optic nerve head and choroid and is of considerable significance in explaining the site of the lesion and the pathogenesis of these defects.

Material and methods

Fluorescence fundus angiography was performed in 24 eyes of rhesus or cynomolgus monkeys after an injection of 0·15 ml. of 5 per cent. fluorescein solution into the common carotid artery on the same side. The fundus was photographed serially every 0·8 second, by a Zeiss fundus camera adapted for fluorescence angiography, from the time of injection to the end of the transit of the dye. Several fluorescence angiographies were done on the same eye.

In eight of these 24 eyes fluorescence angiography was done after an experimental occlusion of the central retinal artery, in order to make the choroidal circulation more clearly visible (Hayreh and Perkins, 1969; Hayreh, 1969).

Observations

The pattern of the choroidal filling was recorded in all these eyes. Normally the choroidal bed fills up about a second or so before the retinal circulation. Once the retinal circulation fills up, it completely masks the underlying choroidal bed. In sixteen eyes the pattern of filling of the choroidal vascular bed was studied during this very short time interval between the retinal and choroidal fillings. In the remaining eight eyes, the retinal circulation was completely eliminated by an experimental occlusion of the central retinal artery in the orbit before fluorescence angiography, and this allowed a detailed study of the choroidal vascular bed without any masking effect by the retinal circulation (Hayreh, 1969; Hayreh and Perkins, 1969).

In ten eyes the whole of the choroidal vascular bed did not fill simultaneously; a part of the bed filled before the rest. This was due to the difference in the circulation time of the different posterior ciliary arteries. This difference in the circulation time made it possible to outline the distribution of the different posterior ciliary arteries in the choroid

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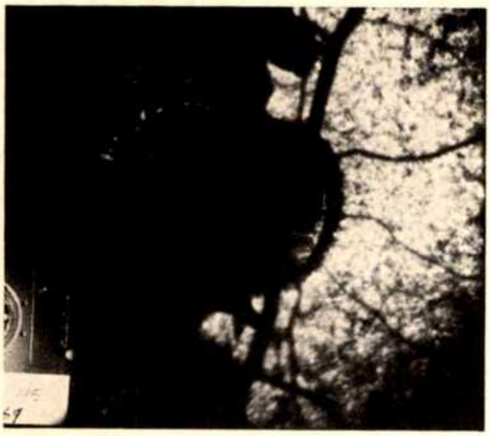
and the optic disc. The distribution of these arteries showed the following patterns in the present study:

(a) In 80 per cent. the temporal and nasal parts of the choroid filled separately—more often the temporal part before the nasal part. The ciliary supply to the optic disc filled with the respective parts of the choroid, so that it was possible to outline the territory of the optic disc supplied by the posterior ciliary artery. This is illustrated in Figs 1, 2, 3, 4, and 5*a*.

(1)



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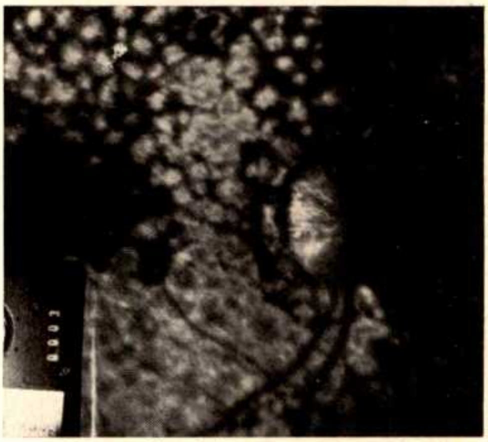
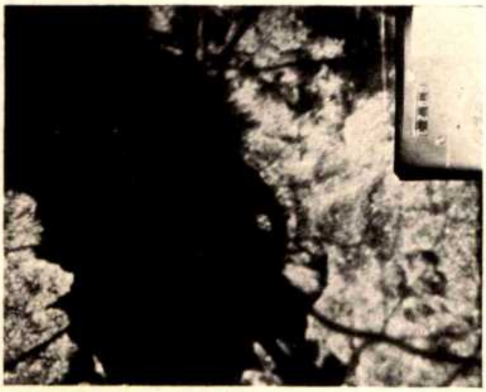


FIG. 1 *Fluorescence fundus angiogram of right eye of a cynomolgus monkey during pre-retinal-arterial phase, showing a well-demarcated filling of nasal half of choroid and prelaminar vessels in nasal part of optic disc*

FIG. 2 *Fluorescence fundus angiogram of right eye of a cynomolgus monkey during the pre-retinal-arterial phase, showing filling of temporal half of choroid and prelaminar vessels in temporal part of optic disc*

(3)



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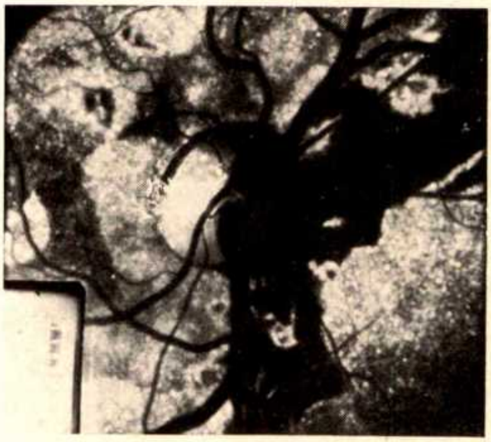

FIG. 3 *Fluorescence fundus angiogram of left eye of a cynomolgus monkey during the pre-retinal-arterial phase, showing filling of the temporal half of the choroid with an early filling of some of the prelaminar vessels in the optic disc from the choroid. Note an early filling of the inferior nasal part of the choroid with the peripapillary zone not yet filled*

FIG. 4 *Fluorescence fundus angiogram of right eye of a cynomolgus monkey after experimental occlusion of the central retinal artery. The lateral posterior ciliary artery supplies the temporal half and the superior nasal part of the choroid. Early filling of the medial posterior ciliary artery in the inferior nasal sector of the choroid is seen. The border zone between the two and the nasal peripapillary region is still not filled. Part of the optic disc supplied by the lateral posterior ciliary artery is filled*

The medial posterior ciliary arteries usually supplied about half of the choroid and the lateral posterior ciliary arteries supplied the other half (Figs 1, 2, 3, and 5*a*), but sometimes one more than the other (Fig. 4). The areas of distribution by the two posterior ciliary arteries remained separate for some time with little communication between the two (Fig. 4). One received the impression that the choroidal vascular bed was not a freely communicating bed but tended to have a sectoral distribution. The same applied to the distribution of the arteries in the optic disc.

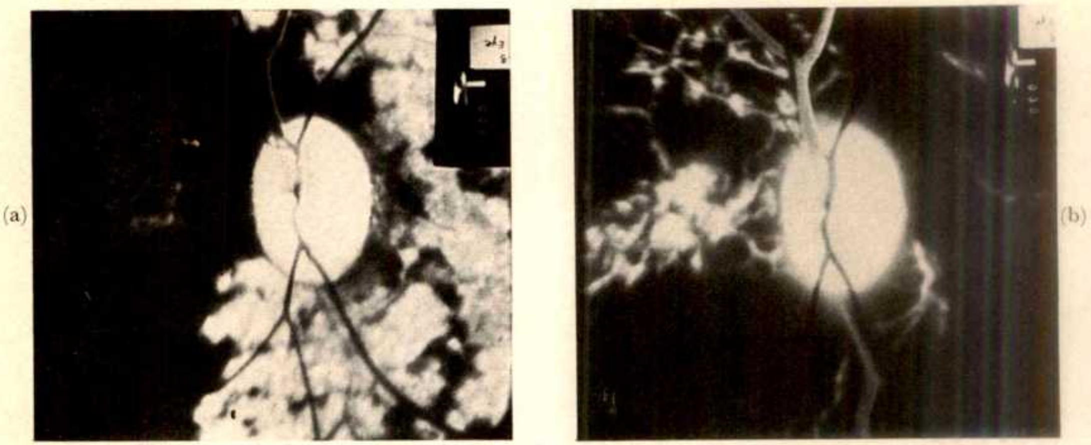

FIG. 5. *Fluorescence fundus angiograms of left eye of a cynomolgus monkey after experimental occlusion of the central retinal artery:*

(*a*) Filling of the temporal half of the choroid,
(*b*) Another angiogram during the early stages showing filling of the superior nasal quadrant only.
Marked fluorescence of the optic disc in (*a*) and (*b*) is due to previous injections of fluorescein.

(b) In 20 per cent. the upper and lower parts of the choroid and optic disc filled separately, with a sharp horizontal line of demarcation (Fig. 6, and Fig. 7, overleaf). Here again no free communication could be detected in their distribution.

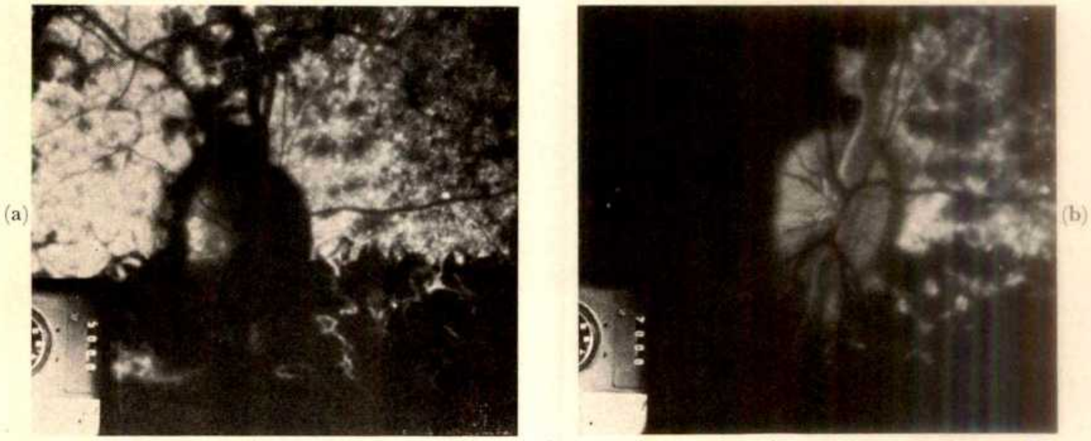

FIG. 6 *Fluorescence fundus angiograms of right eye of a cynomolgus monkey after experimental occlusion of the central retinal artery:*

(*a*) First angiogram, showing filling of upper half of choroid and optic disc with a well-demarcated horizontal border
(*b*) Second angiogram, showing filling of superior nasal quadrant at first. The marked fluorescence of the optic disc in (*b*) is due to the previous injection of fluorescein.

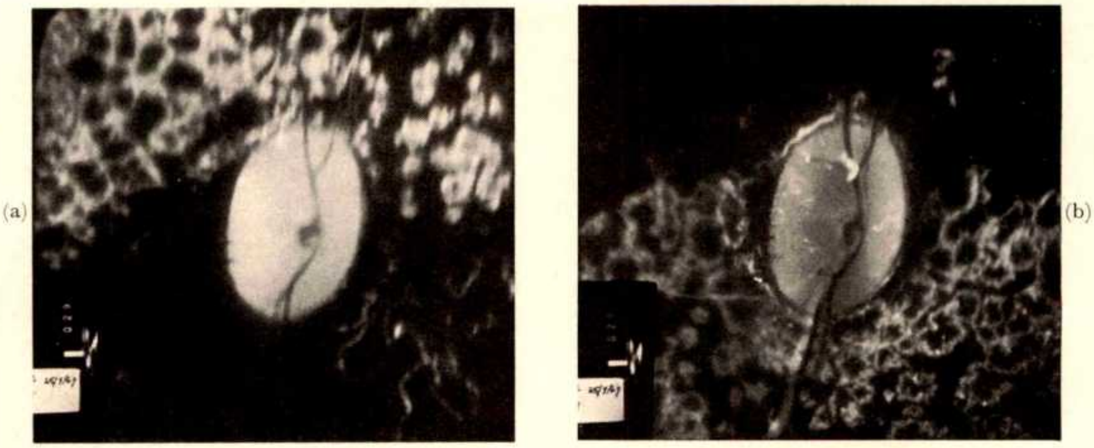

FIG. 7 *Fluorescence fundus angiograms of right eye of a cynomolgus monkey after experimental occlusion of the central retinal artery:*

(*a*) Filling of upper half of choroid at first.

(*b*) Another angiogram showing filling of lower half of choroid at first. The marked fluorescence of the optic disc in (*a*) and (*b*) is due to previous injections of fluorescein

(c) On repeated fluorescence angiography in the eyes seen in **(a)** and **(b)** above, it was possible to see in some a further sectoral filling of the choroid and the optic disc. This was mainly quadrantic in pattern, as shown in Figs 5*b* and 6*b*.

Discussion

The observations of the present study *in vivo*, that the posterior ciliary arteries have a segmental distribution in the choroid and optic disc, would help to explain the mechanism of some of the visual field defects which have been ill-understood so far. Before discussing these, it is essential to describe briefly the pattern of the posterior ciliary arteries in man, and the blood supply of the optic disc and optic nerve, in order to make the discussion explicit.

POSTERIOR CILIARY ARTERIES

A detailed account of the pattern of the posterior ciliary arteries in man has been given elsewhere (Hayreh, 1962a). Briefly, the posterior ciliary arteries can be designated medial, lateral, or superior, according to their relationship to the optic nerve near the eyeball (Fig. 8). The ophthalmic artery may give out one (in 3 per cent.), two (in 48 per cent.), three (in 39 per cent.), four (in 8 per cent.), or five (in 2 per cent.) posterior ciliary arteries of varying sizes.

(*a*) *Medial posterior ciliary arteries* may be one (in about 70 per cent.) or two (in about 30 per cent.).

(*b*) *Lateral posterior ciliary arteries* may be one (in about 75 per cent.), two (in about 20 per cent.), three (in less than 2 per cent.), or none (in about 3 per cent.).

(*c*) *Superior posterior ciliary arteries* are seen in only 9 per cent. and may be one (in 7 per cent.) or two (in 2 per cent.). These are usually small in size.

The mode of origin of the posterior ciliary arteries from the ophthalmic artery varies. The medial posterior ciliary arises in common with the central retinal artery in 44 per

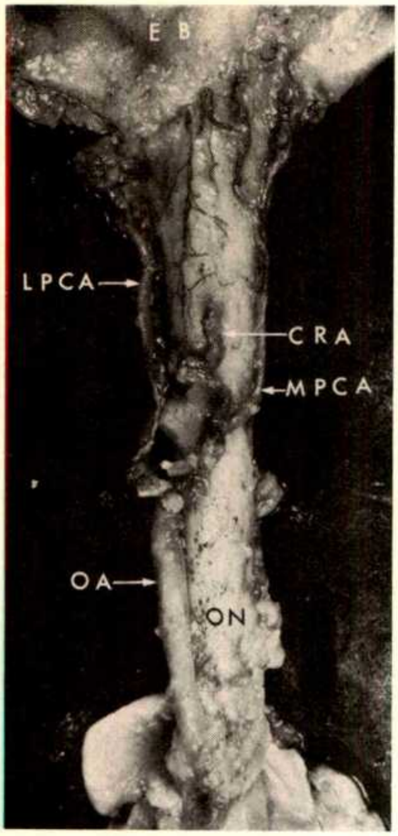

FIG. 8 *Photograph of inferior surface of optic nerve (ON) and eyeball (EB), showing ophthalmic artery (OA), central retinal artery (CRA), and medial (MPCA) and lateral (LPCA) posterior ciliary arteries*

cent. of cases (Fig. 8). In the remainder it usually arises alone and occasionally with other branches of the ophthalmic artery. The lateral posterior ciliary artery arises with the central retinal artery in only 12 per cent. of cases; in the remainder usually as an independent branch, and very rarely with any other branch. When the ophthalmic artery crosses over the optic nerve in the second part of its course in the orbit, the medial posterior ciliary artery is the first branch of the artery in 53 per cent. of cases (Fig. 8), and the lateral posterior ciliary in 22 per cent. On the other hand, when the ophthalmic artery crosses under the optic nerve in the orbit (in 17·4 per cent.), the lateral posterior ciliary artery is the first branch of the artery in 91·3 per cent. and the medial posterior ciliary is never the first branch.

The posterior ciliary arteries run forwards, divide into ten to twenty small branches (Wolff, 1948; Duke-Elder, 1961) and pierce the sclera near the optic nerve. Out of these large numbers of branches of the posterior ciliary arteries, one on the medial and another one on the lateral side form the long posterior ciliary arteries, while the rest are called the short posterior ciliary arteries. The two long posterior ciliary arteries pierce the sclera on the medial and lateral sides slightly further away from the optic nerve than the short ones. A retrospective study of the photographs of about a dozen specimens, given by Hayreh (1958), indicates that the lateral posterior ciliary arteries usually pierce the sclera lateral or supero-lateral to the optic nerve, while the medial posterior ciliary arteries pierce the sclera medial or infero-medial to the nerve (Fig. 8). This information, however, needs further confirmation. The posterior ciliary arteries are usually markedly tortuous.

BLOOD SUPPLY OF THE OPTIC DISC

This is given in detail elsewhere (Hayreh and Perkins, 1968, 1969; Hayreh, 1969). Briefly, the lamina cribrosa region is supplied by centripetal branches from the short posterior ciliary arteries, either by direct branches or, less frequently, through the so-called arterial circle of Zinn and Haller (Fig. 9).

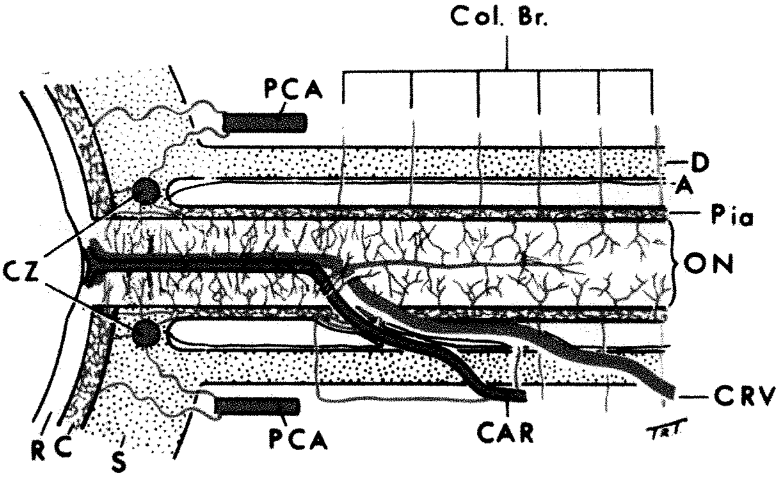

FIG. 9 *Pattern of blood supply of optic nerve in man*

A	Arachnoid
C	Choroid
CAR	Central artery of the retina
Col. Br.	Collateral branches of ophthalmic artery
CRV	Central retinal vein
CZ	Circle of Zinn
D	Dura
ON	Optic nerve
PCA	Posterior ciliary arteries
R	Retina
S	Sclera

The prelaminar region is supplied by centripetal branches from the adjacent peripapillary choroid (Figs 1, 2, 3, 4, 6*a*, 9, and 11). The part containing the papillomacular bundle is much more vascular than the rest (Figs 2 and 4).

The surface nerve fibre layer of the disc is supplied by the retinal arterioles; sometimes the temporal sector of this receives a contribution from the underlying ciliary vessels of the prelaminar region.

Thus, the *main source of blood supply to the optic disc is derived from the ciliary circulation.* As far as one can judge, the ciliary contribution to the disc by the various short posterior ciliary arteries tends to be sectoral.

BLOOD SUPPLY OF THE INTRAORBITAL PART OF THE OPTIC NERVE

A detailed account of this is given elsewhere (Hayreh, 1958, 1962b, 1963a, b, 1964; Singh and Dass, 1960). Briefly, the intraorbital part of the optic nerve can be divided into two parts when considering its blood supply:

(*a*) *The anterior segment* containing the central retinal vessels in its centre.

(*b*) *The posterior segment* which lies behind (*a*).

(*a*) *The anterior segment*

This contains axial and peripheral vascular systems (Fig. 9).

(1) *Axial centrifugal vascular systems:* This is seen in 75 per cent. of the cases and is always formed by the intraneural branches of the central retinal artery and *not* by the so-called "central artery of

the optic nerve". The axial system supplies the centre of the optic nerve to a variable extent in this part of the nerve.

(2) *Peripheral centripetal vascular system:* This is present in 100 per cent. of the cases and is formed by (*i*) multiple recurrent pial branches all round the retrolaminar part of the optic nerve from the peripapillary choroidal vessels and some from the circle of Zinn and Haller; (*ii*) pial branches from the central retinal artery on the inferior (in 100 per cent.), lateral (in 50 per cent.), medial (in 39 per cent.) and superior (in 18 per cent.) surfaces of the optic nerve; and (*iii*) pial branches from the ophthalmic artery or its various intra-orbital branches. The distributions of (*ii*) and (*iii*) are reciprocal.

(*b*) *The posterior segment*

In this part of the optic nerve no axial centrifugal vascular system exists except for a very rare small recurrent branch from the central retinal artery, which may run back in the centre of the nerve in the posterior segment for about 2 to 3 mm. only. The whole of this segment is supplied by the peripheral centripetal vascular system (Fig. 9). This is formed by the pial vessels which usually arise direct from the ophthalmic artery and, less commonly, from the central retinal, medial muscular, medial posterior ciliary, posterior ethmoid, supraorbital, or other muscular arteries. These usually number one to three, rarely more. They are much less commonly situated on the lateral surface of the optic nerve.

I want to stress here that the "central artery of the optic nerve", as described by François and Neetens (1954, 1956) and François, Neetens, and Collette (1955), has never been seen by me in over a hundred human specimens, and that this has been further confirmed by a large number of workers.

SEGMENTAL DISTRIBUTION OF THE POSTERIOR CILIARY ARTERIES

Wagenmann (1890) thought, from his studies in rabbits, that the distribution of the short posterior ciliary arteries in the choroid was strictly segmental and that these arteries were functional end-arteries. Leber (1903) was of a similar opinion and emphasised the lack of anastomoses between the different branches of these arteries except in the peripapillary region and in the extreme periphery of the choroid. Coats (1907) and Hepburn (1912), from dubious clinical observations, subscribed to the idea of the segmental pattern of the choroidal vascular supply. Wybar (1954a,b), basing his opinion on his injection studies of the short posterior ciliary arteries, concluded that these arteries were segmentally arranged and that each branch supplied a localized zone of the choroid with an arteriolar-capillary network, but he denied any anatomical evidence for the concept that these arteries were true end-arteries. He injected seven eyes through the ophthalmic artery, after occlusion of a single short posterior ciliary artery. In four eyes the choroid was completely filled but, in the other three eyes, a partial sectoral filling defect occurred in the choroid which corresponded in situation to the blocked short posterior ciliary artery. On injection of a single short posterior ciliary artery immediately behind the eyeball in two eyes, he was unable to inject the entire choroid. He, however, regarded the filling defects in the last five eyes as artefacts.

In the present study *in vivo*, a well demarcated segmental distribution by the posterior ciliary arteries in the choroid and the optic disc was seen in ten of 24 eyes. In 80 per cent. of these eyes the temporal or nasal half of the choroid and the optic disc filled with the dye completely, while the other half showed a complete absence of filling; the areas of filling and non-filling were sharply outlined (Figs 1, 2, 3, and 5). In the remaining 20 per cent. of eyes, a similar phenomenon was seen in the upper or lower half of the choroid and optic disc (Figs 6 and 7) instead of the temporal or nasal half. On repeated fluorescence angiography in these ten eyes, in some only a quadrantic filling of the choroid and optic disc was seen, the rest being completely empty (Figs 5*b* and 6*b*). The fact that such a segmental distribution could not be outlined in all the 24 eyes does not necessarily mean that it was absent in the rest. This is because the ability to outline areas of supply by different posterior ciliary arteries by means of fluorescence angiography depends upon there being some difference in the circulation time in the different posterior ciliary arteries. When there is no such difference in the circulation time, the areas supplied by the various posterior ciliary arteries fill simultaneously, and it is impossible to outline the distribution by the individual posterior ciliary artery or the short posterior ciliary arteries. The other difficulty with the present technique is that it is impossible to take fluorescence angiographic pictures faster than 0·8 second with the Zeiss equipment, and this is too long a time interval to outline individual arteries with difference in circulation time of less than 0·8 second. This is illustrated by the fact that in some cases in which one transit of the dye showed a filling of half of the choroid and the disc, in another transit it was possible to outline only a quadrantic filling (Figs 5*b* and 6*b*). These studies *in vivo* thus suggest a *well-demarcated segmental distribution by the posterior ciliary arteries in the choroid and the optic disc.* This is further suggested by the selective localization of pathological lesions in the choroid and the disc in relation to its vascular anatomy. Some of the optic disc lesions in this category are discussed in this paper.

NERVE FIBRE BUNDLE DEFECTS

The term "nerve fibre bundle" refers to any small group of nerve fibres which lie together as they enter the optic disc (Traquair, 1944). The most classical visual field defect produced by nerve fibre bundle defects is the arcuate scotoma (Bjerrum scotoma, comet scotoma, scimitar scotoma). Though it is classically described in glaucoma, it is also seen in a large variety of lesions of the retina, optic nerve, optic disc, juxtapapillary choroiditis, myopia, etc. Cases showing the nerve fibre bundle defects due to a large number of causes have been reported by Harrington (1964a). It can assume a great variety of shapes and positions.

Nerve fibre bundle defects have been extensively investigated (Meisling, 1900; Friedenwald, 1902; Sinclair, 1905; Rønne, 1909, 1915, 1927; Traquair, 1944; Dubois-Poulsen and Magis, 1955, 1956; Dubois-Poulsen, 1952, 1956; Harrington, 1959, 1960, 1964a, b; and Hoyt, 1962; and others). Hoyt (1962), on tracing degeneration of the nerve fibres in the optic nerve after experimental retinal lesions in the Bjerrum area, found the distribution of degeneration from the upper and lower arcuate bundles located in the temporal half of the optic nerve, in a wedge-shaped area behind the lamina cribrosa, extending up to the central retinal vessels. These findings agreed in general with topographic fibre organization of the optic nerve described by Parsons (1902), Brouwer and Zeeman (1926), and Polyak (1957), though none of these described the arcuate bundles specifically.

The pathogenesis of nerve fibre bundle defects in glaucoma is described elsewhere. These defects may also be produced by inflammatory, traumatic, and vascular lesions of the optic disc and optic nerve, vascular lesions being considered by the majority to be by far the commonest cause. The site of the vascular lesion and the vessels involved has, however, proved a highly controversial matter.

Dubois-Poulsen and Magis (1954) found that the Bjerrum scotoma was not pathognomonic of glaucoma and might be found in many lesions affecting the visual pathways anterior to the lateral geniculate body. They added that it corresponded to a well-separated bundle of nerve fibres and that its cause must be vascular and extraocular. They thought that the actual lesion might be located immediately posterior to the eyeball in the arterial circle of Zinn and Haller or further back in the optic nerve. They did not think that raised intraocular pressure had any role to play in the pathogenesis of the lesion in glaucoma. Harrington (1964a,b) stated that interference with the vascular supply of the anterior optic nerve in the region of the circle of Zinn and Haller might also give rise to nerve fibre bundle defects which could be indistinguishable from the field defects of glaucoma.

The vascular lesions responsible for nerve fibre bundle defects lie either in the optic disc or in the optic nerve. Since the centripetal vessels in the optic disc and optic nerve are radial and have a segmental supply, these would involve the nerve fibres in a sectoral fashion. In the optic disc there is no centrifugal vascular system and blood supply by the individual subdivisions of the posterior ciliary arteries to the nerve head is of a better defined sectoral type than that in the retrobulbar optic nerve. Moreover, the arrangement of nerve fibres in the optic disc topographically is presumably more representative of the retinal arrangement than that in the intraorbital part of the optic nerve. A typical nerve fibre bundle defect is, therefore, far more likely to arise from an optic disc lesion than from a posterior optic nerve lesion.

In the past, attention has been mainly focused on the lamina cribrosa region as the site of vascular occlusion by involvement of branches of the circle of Zinn or of the retrobulbar part of the optic nerve. Since the circle of Zinn is not commonly found, its distribution is generally taken over by direct branches from the posterior ciliary arteries themselves. These have a sectoral distribution in the region of the lamina cribosa with little anastomoses between the adjacent arteries. Similarly, in the prelaminar region, it seems that each branch of the posterior ciliary arteries supplies a well-defined sector. The involvement of one of these arteries thus produces a sectoral nerve fibre bundle defect. The retrolaminar part of the optic nerve obtains its centripetal peripheral blood supply from the recurrent pial branches from the choroidal vessels and the circle of Zinn (Fig. 9). Occlusion of one of the posterior ciliary arteries or its smaller subdivisions, therefore, would involve a sector of the lamina cribrosa, the prelaminar part of the optic disc, and the retrolaminar part of the optic nerve (Fig. 9). When a sector of the peripapillary choroid only is involved, the region of the lamina cribrosa may be spared.

An occlusion of one of the pial nutrient vessels from the ophthalmic artery or of one of its intraorbital branches behind the retrobulbar part of the optic nerve (Fig. 9) produces a localized infarct and a scotoma in the region of the nerve fibres involved, but the choroidal circulation has no role to play in these lesions situated in the orbit behind the retrobulbar part.

In arteriosclerotic optic atrophy, it is usually thought that the lesion lies in the nutrient vessels of the optic nerve. I feel that it could equally well be due to arteriosclerotic changes in the posterior ciliary vessels which involve the optic nerve head and the area immediately behind the lamina cribrosa, producing nerve fibre bundle defects, optic atrophy, and cupping of the disc. This may simulate glaucoma, the mechanism of which is discussed on p. 301. In these cases there may even be sector defects and peripheral constriction (Parin, 1951; Hughes, 1958; Peters, 1958).

A posterior ciliary artery occlusion may also result from any form of arteritis (*e.g.* temporal arteritis) or embolism or arteriosclerosis. This would produce infarction of the optic disc and the adjacent optic nerve; the area involved depends upon the size of the artery occluded, *i.e.* the occlusion of the main posterior ciliary artery involves a larger area of the optic nerve head, but involvement of one of the smaller subdivisions leads to a sectoral lesion (Hayreh, 1969). The size and distribution of the nerve fibre bundle defects depend upon the area of the optic nerve head involved. In these cases the retinal vessels are normal. Fig. 10 shows an example of a nerve fibre bundle defect, indistinguishable from glaucoma, seen in a patient with temporal arteritis and sectoral involvement of the optic disc with a normal retina.

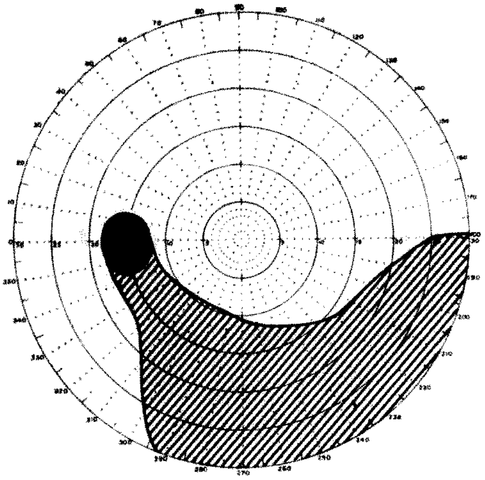

FIG. 10 *Visual field defect in the left eye of a 66-year-old woman with temporal arteritis (reproduced by courtesy of Dr. J. F. Cullen from one of his cases). Target 5/2000 white. Visual acuity 6/9*

In myopia, nerve fibre bundle defects may be due either to chorioretinal atrophy near the optic disc, or to a marked peripapillary choroidal atrophy in one sector which interferes with the blood supply to the corresponding sector of the disc. These result in a Bjerrum scotoma, etc. Similarly, juxtapapillary choroiditis may produce nerve fibre bundle defects by either of the two mechanisms mentioned in myopia.

Hence any lesion destroying the peripapillary choroid in a sector would interfere with the blood supply of the optic disc and result in the nerve fibre bundle defect in the corresponding sector. Also any lesion blocking a posterior ciliary artery would produce ischaemia of a sector of the optic disc and maybe of the adjacent optic nerve and produce the nerve fibre bundle defect; in these cases a secondary peripapillary choroidal atrophy is also produced by the vascular occlusion. Hoyt (1962) described two cases of the latter variety with arcuate scotoma, peripapillary choroidal atrophy, and sectoral optic atrophy in the inferior temporal sector, which he rightly attributed to occlusion of the posterior ciliary arteries.

In incomplete occlusion of the posterior ciliary artery, the imbalance induced between the normal intraocular pressure and the low blood pressure in the disc vessels of choroidal origin would produce a classical picture of glaucoma (*see* p. 301). These cases in the past have been called "low tension glaucoma" or pseudoglaucoma (*see* p. 301). Thus, *a complete occlusion of the posterior ciliary arteries produces ischaemic optic neuropathy, while an incomplete occlusion produces glaucomatous changes.* In both cases the nerve fibre bundle defects are identical.

VISUAL FIELD DEFECTS IN GLAUCOMA

Classically the diagnostic visual field defect in glaucoma is the nerve fibre bundle defect. In addition to this there may be a general depression with peripheral contraction, especially in the superior nasal quadrant, and enlargement, elongation, and baring of the blind spot. Central vision is retained until a late stage.

The subject of the pathogenesis of visual field defects, especially the nerve fibre bundle defects in glaucoma has, since their first description a century ago by Landesberg (1869) and later by Bjerrum (1889), been a matter of great interest and controversy. It is discussed in detail elsewhere (Hayreh, 1969; Hayreh, Revie, and Edwards, 1970), and only a brief résumé will be given here. Various views on the subject can be classified in two main categories:

(*A*) *Neurogenic origin*

This has been considered by many authors, the latest contribution being that of Smith (1965), according to whom the field defects are due to direct damage to the optic nerve fibres on the optic disc by the raised intraocular pressure and distortion occasioned by partial collapse outwards of the lamina cribrosa. Smith thought that the most important single factor is the loss of the normal plane of the lamina cribrosa, producing a sharp kinking of the nerve fibres.

(*B*) *Vasogenic origin*

This has been suggested by many workers*. Harrington (1964a, b) concluded that, in glaucoma, the nerve fibre bundle defects are produced by anything that upsets the normal balance between the intraocular pressure and the retinal or ophthalmic arterial pressure, resulting in decreased blood flow in the anterior optic nerve in the region of the lamina cribrosa and the arterial circle of Zinn and Haller. More or less similar was the opinion of Drance and others (1968). Hayreh (1969) concluded from experimental studies (Hayreh and Perkins, 1968, 1969) that the relationship between the blood pressure in the prelaminar centripetal vessels in the optic disc (derived from the ciliary circulation) and the intraocular pressure determines the state of patency of these vessels and that there exists a critical balance; lowering of the blood pressure or elevation of the intraocular pressure has a similar effect. This was further confirmed in subsequent studies by altering one of these two pressures and keeping the other constant (Hayreh and others, 1970). The retinal circulation did not play any role in this, which contradicts the views of Henkind (1967a, b) and those of Kornzweig and others (1968).

Fig. 11 (overleaf) shows schematically the arrangement of blood vessels in the prelaminar part of the optic disc. Their distribution is segmental in the disc, so that obliteration of these, or of the adjacent peripapillary choroid (Fig. 12) from which they arise, could produce nerve fibre bundle defects. The studies revealed that the choroidal contribution to the blood supply of the optic disc is the most susceptible to obliteration by raised intraocular pressure; next in susceptibility is the peripapillary choroid (Fig. 12). The rest of the choroid shows less susceptibility to obliteration and the retinal circulation showed no susceptibility at all. A much higher incidence of peripapillary choroidal atrophy in patients with glaucoma than is seen ordinarily in persons in the same age group seems to offer further evidence in support of this view. There is a suggestion that certain sectors of the vascular supply to the optic disc from the choroid are more susceptible than the others (Hayreh, 1969; Hayreh and Perkins, 1969).

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* Troncoso (1902), Morax (1916), Elschnig (1928), Magitot (1929), Lauber (1936), Evans (1939), Reese and McGavic (1942), Weekers (1942), Traquair (1944), Sjögren (1946), McGuire (1948), Beauvieux (1948), Sanna (1950), Cristini (1951), Duke-Elder (1953, 1955, 1957), Dubois-Poulsen and Magis (1955, 1956), Redslob (1955, 1957), Gafner and Goldmann (1955), Leydhecker (1955), Dubois-Poulsen (1956), Nordmann (1956), McLean (1957), Niedermeier (1957), Harrington (1959, 1964a, b), Drance (1962a, b), Francois and Neetens (1964, 1966), Kalvin, Hamasaki, and Gass (1966), Hamasaki and Fujino (1967), Henkind (1967a, b), Drance, Wheeler, and Pattullo (1968), Ernest and Potts (1968, 1969), Alterman and Henkind (1968), Kornzweig, Eliasoph, and Feldstein (1968), Hayreh and Perkins (1968, 1969), Hayreh (1969), and others.

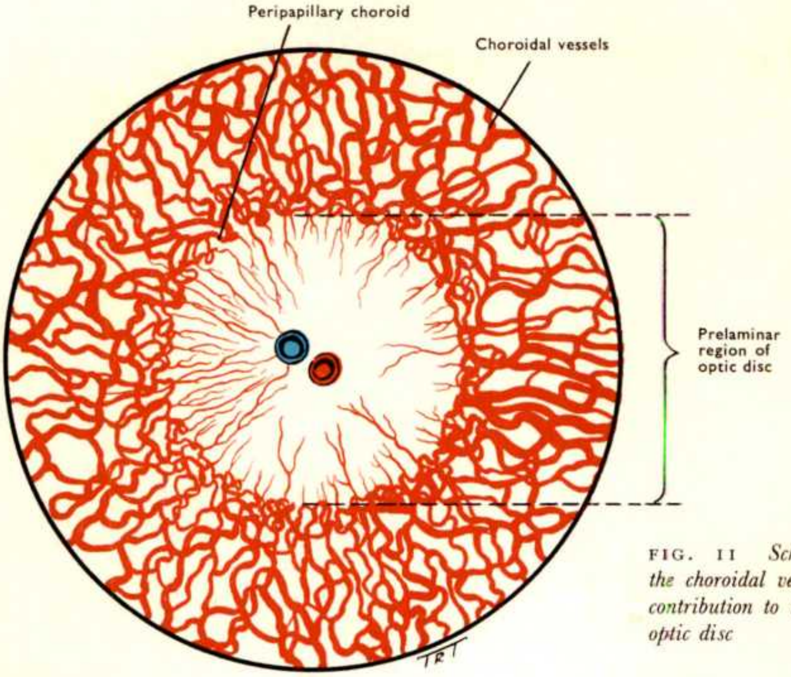

FIG. 11 *Schematic representation of the choroidal vessels and their centripetal contribution to the prelaminar part of the optic disc*

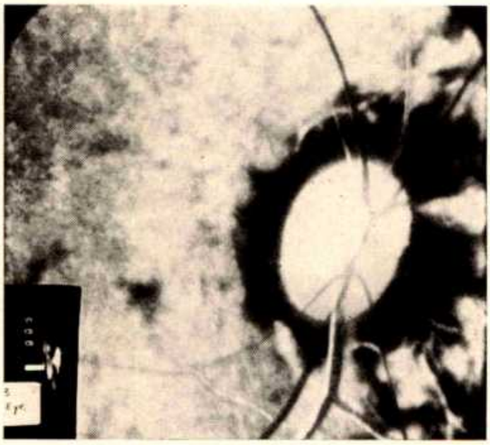

FIG. 12 *Fluorescence fundus angiogram of right eye of a cynomolgus monkey after experimental occlusion of central retinal artery and 70 mm. Hg intraocular pressure. It shows obliteration of the peripapillary choroid all round the optic disc. Fluorescence of the disc is due to previous injections of fluorescein*

The involvement of the peripapillary choroid in glaucoma (Fig. 12) would produce not only changes in the prelaminar part of the optic disc (Fig. 11), but also ischaemic changes in the retrolaminar part of the optic nerve, because of the recurrent pial branches arising from this part of the choroid supplying the retrolaminar part of the optic nerve (Fig. 9). Since the pial branches in this part of the optic nerve contribute to the peripheral centripetal vascular system, their involvement could produce contraction of the peripheral visual fields and ultimately the cavernous degeneration of this part of the optic nerve, both due to ischaemia of the peripheral part of the retrolaminar part of the optic nerve.

From these studies, *it is postulated that* **(a)** *the site of the lesion in the nerve fibre bundle defects in glaucoma lies in the optic disc and, for the peripheral contraction of the fields, possibly in the peripheral part of the retrolaminar part of the optic nerve; and that* **(b)** *this is due to the involvement of the choroidal supply to the disc and the retrolaminar part of the optic nerve as a result of disturbed balance between the arterial blood pressure in these choroidal vessels and the intraocular pressure.*

LOW TENSION GLAUCOMA OR PSEUDOGLAUCOMA

This is a type of glaucoma in which, instead of raised intraocular pressure, there is a fall in blood pressure in the ciliary vessels leading to the same end-results as glaucoma. One variety of this type of glaucoma is arteriosclerotic optic atrophy, in which the fall in blood pressure in the optic disc vessels, caused by arteriosclerotic changes in the posterior ciliary vessels, upsets the normal balance between the intraocular pressure and the blood pressure in the disc vessels. This produces glaucoma. Arteriosclerotic changes in the posterior ciliary arteries may, therefore, be a cause of glaucoma and all the associated changes and clinical findings of glaucoma, thus making arteriosclerotic optic atrophy just another variety of glaucomatous optic atrophy. Carotid artery stenosis, which produces low ophthalmic artery blood pressure resulting in low ciliary artery blood pressure, has the same effect. In these cases even emboli from the carotid plaques may occlude the posterior ciliary artery or its finer branches to the optic disc and thus produce the nerve fibre bundle defects.

From these observations one could define glaucoma as a disease in which the normal balance between the intraocular pressure and the blood pressure in the choroidal vessels supplying the optic disc and the retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and the retrolaminar part of the optic nerve, which produces visual field defects and optic disc and optic nerve changes.

PRECHIASMAL ALTITUDINAL HEMIANOPIA

In this discussion we are concerned only with those altitudinal hemianopias which are of prechiasmal origin with no abnormality in the retina. These are seen in:

Arteriosclerotic optic atrophy (Hughes, 1954; Harrington, 1964b),

Arterial hypertension.

Following massive haemorrhages (*see* p. 305),

Temporal arteritis (Schmidt, 1930; Wagener, 1946; Benedict, Wagener, and Horton, 1957; Piper and Unger, 1957; Wagener and Hollenhorst, 1958; Cullen, 1967),

Ischaemic optic neuropathy (also called arteriosclerotic papillitis, opticomalacia, vascular pseudopapillitis or papillary apoplexy) (Piper and Unger, 1957; Cullen, 1967),

Papilloedema (Walker and Cushing, 1916; Cogan, 1966),

Angioma of the optic nerve head (Hughes, 1958),

Tabes with primary optic atrophy (Walsh, 1957; Harrington, 1964b),

Arteriosclerosis of the internal carotid artery (Knapp, 1940),

Indirect injuries of the optic nerve (Hughes, 1958),

Other causes involving the optic nerve.

Hemianopia usually occurs in the lower visual field and less commonly in the upper half. The demarcation line lies horizontally and may not be absolutely straight. A generalized depression of the preserved field may also be seen.

The pathogenesis of these defects has evoked many ingenious hypotheses. The views of Wolff (1935) and Hughes (1958) are mentioned in the discussion on post-haemorrhagic amaurosis (p. 306). Piper and Unger (1957) thought that they were due to acute circulatory disorders of the optic nerve in post-haemorrhagic amaurosis and ischaemic optic neuropathy. They were of the opinion that occlusion of the distal part of the anterior branch of the central artery of the optic nerve caused an anaemic infarct in the lamina cribrosa region where the fibres from the upper half of the retina run. However, it has now been fairly conclusively proved that the central artery of the optic nerve is rarely if ever present in man (Hayreh, 1963a, b).

Harrington (1964b) suggested that injury to the blood supply of the optic nerve produced altitudinal hemianopia, usually inferior. He proposed a sharp division of the optic nerve into three areas based on its blood supply—superior peripheral, inferior peripheral, and central. He further stated that the vascular supply to the optic nerve came through a network of vessels in the arachnoid membrane, which passed through the subarachnoid space and entered the optic nerve at right angles. In its upper part the space is narrow and the vessels that traverse it from the membrane to the nerve are short and easily damaged by torsion, oedema, and other injury. This, according to Harrington, gives rise to a unilateral altitudinal field defect with horizontal border, steep edges, and great density. My detailed anatomical studies on the subject of the blood supply of the optic nerve (Hayreh, 1958, 1962b, 1963a,b, 1964) mentioned above, and also those of the other workers on the subject, in no way support any of Harrington's speculations. Hughes (1958) rightly pointed out that there was no evidence of a horizontal or vertical division of the blood supply of the optic nerve, apart from the central-peripheral separation. He stated, however, that these field defects strongly suggested some segmental arterial supply in the optic nerve whereby the blood supply of one horizontal half of an optic nerve may be cut off by a single lesion. In many such cases the central area of the field is spared, but in some this also is affected. He stressed that none of the anatomical work reported could provide any explanation for the clinical experience.

Walker and Cushing (1916) suggested that altitudinal hemianopia in papilloedema was due to the intracranial lesion pressing against the upper rim of the optic foramen.

The present studies have clearly demonstrated a hitherto unknown well-demarcated line of division between the upper and lower parts of the choroid and the optic disc with a horizontal boundary line (Fig. 6*a* and 7). Occlusion of one of the two main posterior ciliary arteries, which supplies half of the optic disc and the corresponding choroid, produces an altitudinal field defect with no retinal changes at all. In acute occlusive disorders the corresponding half of the disc will be oedematous at first, with evidence of ischaemic neuropathy in that part of the disc. Later, all cases show optic atrophy of the corresponding half of the disc. *Such a well-defined horizontal localization of blood supply exists only in the optic disc and that too in its ciliary supply and* **not** *anywhere else in the optic nerve. Thus, altitudinal hemianopias of prechiasmal origin and without any retinal lesion are caused by the occlusion of the main posterior ciliary artery which supplies that half of the disc and the choroid.* Choroidal vascular occlusion also produces death of the visual cells in the retina in that area.

It is difficult to give a definite explanation why the upper part of the choroid and optic disc circulation should be far more commonly involved than the inferior part. One can only surmise. When the distribution by the posterior ciliary artery is horizontal, probably the lower half of the choroid and optic disc are supplied by the medial posterior ciliary artery and the upper half by the lateral posterior ciliary artery, as judged form a very limited study of the sites of penetration of the sclera by these arteries (above, p. 293). As mentioned above, the medial posterior ciliary artery usually arises as the first branch of the ophthalmic artery (Fig. 8) in 53 per cent. of cases when the latter crosses over the optic nerve. Because of this the medial posterior ciliary artery probably receives more blood and at a higher pressure than the lateral posterior ciliary artery. The fact that the central retinal artery circulation is intact in these cases would also tend to indicate intact circulation in the medial posterior ciliary artery—both having a common origin from the ophthalmic artery in 44 per cent. of cases (Fig. 8). Also, in about 30 per cent. of cases, another medial posterior ciliary artery arises from the ophthalmic artery medial to the optic nerve, both being of prominent size. It is not essential for the lateral posterior ciliary artery to be completely occluded in such cases to give rise to an inferior altitudinal hemianopia. The normal intraocular pressure would obliterate in the optic disc any vessel of choroidal origin which had a low blood pressure. In this way the vessels in half of the optic disc could be obliterated, either by complete occlusion of the main posterior ciliary artery supplying that area, or by the obliterative effect of a normal intraocular pressure on a very low blood pressure in the prelaminar vessels of that area.

PRECHIASMAL VERTICAL HEMIANOPIA

Hemianopias are always considered to be due to chiasmal or suprachiasmal lesions and are expected to be mostly bilateral. A unilateral hemianopia, when seen, is usually considered to be a precursor of the ultimate bilateral hemianopias.

Unilateral vertical hemianopia has been reported in cases with post-haemorrhagic amaurosis (Scott, 1957; Harrington, 1964b); the line of hemianopia may be irregular (Scott, 1957).

The medial and lateral posterior ciliary arteries usually supply the medial and lateral halves respectively of the choroid and the optic disc with a sharp line of demarcation between the two (Figs 1, 2, 3, and 5). The various lesions mentioned in the altitudinal hemianopias which produce occlusion of the main posterior ciliary arteries may produce a vertical instead of an altitudinal hemianopia, which may be nasal or temporal. If bilateral, it may result in homonymous or heteronymous hemianopias and may be confused with chiasmal or suprachiasmal lesions. The border of the hemianopic field, instead of passing through the fixation point, as in chiasmal and suprachiasmal hemianopias, will pass through the blind spot in the optic disc hemianopias. The nasal hemianopia, therefore, in these cases is most likely to be accompanied by a central scotoma due to the involvement of the papillo-macular bundle (Fig. 13*a*–*c*, overleaf). In a case of acute onset, the temporal or nasal half of the disc may be oedematous at first with normal retinal vessels and fundus. Later, optic atrophy of the corresponding half of the disc will be seen in all these cases.

QUADRANTIC FIELD DEFECTS

It has already been seen that the main posterior ciliary artery frequently supplies half of the choroid and optic disc, and this may be the superior or inferior half (Figs 6*a* and 7), or the temporal or nasal half (Figs 1, 2, 3, and 5*a*). Each posterior ciliary divides at some distance from the eyeball into further subdivisions. If it first divides into two, each of these subdivisions may supply a quadrant of the choroid and the disc. Such a quadrantic filling of the choroid by the dye was seen in the present study (Figs 5*b* and 6*b*). Occlusion or stenosis of such a subdivision due to any cause would lead to a quadrantic field defect. During acute vascular occlusion of such a subdivision with resultant infarction, that quadrant of the disc may be oedematous, but later it will be atrophic. The possibility of bilateral quadrantic defects due to this cause has to be borne in mind.

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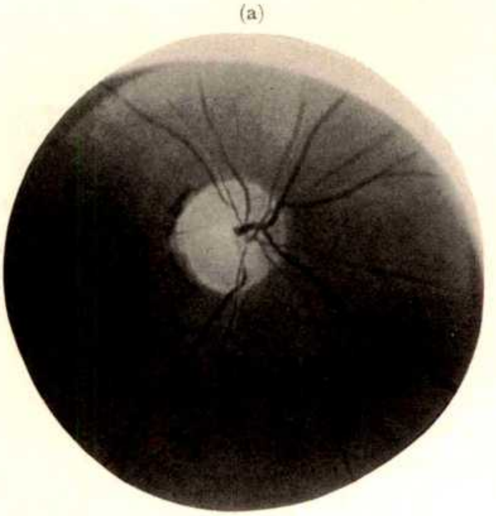

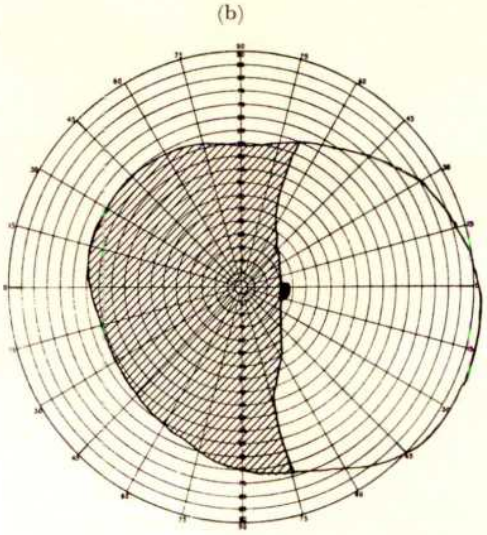

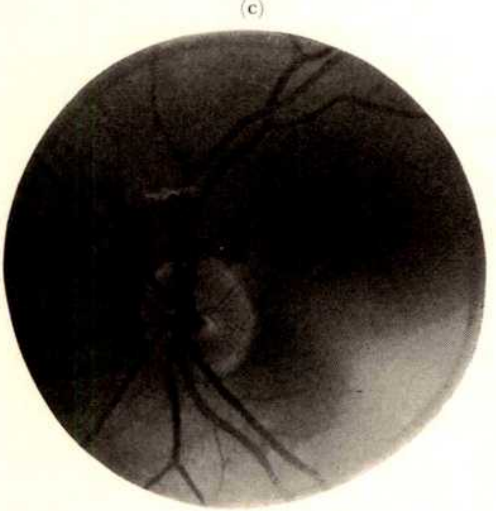

FIG. 13 *A* 67*-year-old woman developed a sudden loss of central vision in the right eye one afternoon* 18 *months ago, which has since remained unaltered. Visual acuity in that eye is now counting fingers in the temporal field; the right disc shows atrophy of the temporal half with a normal nasal half and the retinal vessels show a generalized narrowing—particularly the arteries* (a). *The right peripheral visual fields show a nasal hemianopia with the border of the hemianopic field passing through the blind spot* (b). *The patient was unaware of this right nasal hemianopia. The left eye is normal* (c).

The involvement of still smaller subdivisions of the posterior ciliary artery, supplying a sector of the optic disc, would produce a sectoral field defect.

PERIPHERAL CONTRACTION OF VISUAL FIELDS

The centripetal and centrifugal vascular systems of the optic nerve explain the presence of central and peripheral visual field defects in vascular lesions (Hughes, 1958). The commonest types of field loss in arteriosclerotic optic atrophy are the multiple indentations in the peripheral field, and these most commonly affect the lower field (Hughes, 1958). In tabes the peripheral contraction proceeds towards the centre (Walsh, 1957).

Depression of the peripheral fields in glaucoma is a well-known phenomenon and its pathogenesis is discussed above (p. 300). As mentioned on p. 301, arteriosclerotic optic atrophy seems to be a variety of glaucomatous optic atrophy, with nerve fibre bundle defects and peripheral depression of the fields. The additional factor of involvement of the pial vessels by the arteriosclerotic process may aggravate and complicate the picture. In tabes the peripheral contraction is most probably due to involvement of the pial vessels by a syphilitic process.

POST-HAEMORRHAGIC AMAUROSIS

A large number of cases has been reported in the literature in which visual disturbances, even complete blindness, followed a marked loss of blood. It is interesting to note that Hippocrates was also aware of this when he wrote: "After the vomiting of blackish sometimes bloody matter, the patient complains of headache and eyes do not see". The mechanism of the visual disturbances and the field defects, particularly the altitudinal hemianopias, is still unknown.

Amaurosis is mostly known to follow haemorrhages from the gastrointestinal tract and uterus and less often from the nose, lungs, kidneys, wounds, etc. (Singer, 1904; Pröll, 1907; Bistis, 1908; Alt, 1912; Hegner, 1912; Calhoun, 1913; Pincus, 1919; Görlitz, 1920; Terrien, 1921; Puppel, 1924; Harbridge, 1924; Fink, 1924; Grimminger, 1925; Whiting, 1929; Pines, 1931; Wolff, 1935; Long, 1943; Levatin, 1947; Locket, 1949; Pears and Pickering, 1960; Waldeck, 1960; and others). Small recurrent haemorrhages rather than a single larger one, are mostly responsible for this process.

The visual disturbance varies from blurring to complete loss of vision. It is generally bilateral (in about 90 per cent., Coston, 1935; in 85 per cent., Duke-Elder, 1940). It may be permanent (in 54 per cent., Pergens, 1896; in 45·9 per cent., Singer, 1904; in 50 per cent., Terson, 1922; in 83 per cent., Tidy, 1941) or temporary. It usually starts between the third and seventh days after the haemorrhage (Terson, 1922; Wolff, 1935), but may develop within a few hours (within 24 hours in 30 per cent., Pergens, 1896; within 14 hours in 45 per cent., Groenouw, 1904; within 12 hours in 34·1 per cent., Terson, 1922). The literature has been reviewed by Singer (1904), Terson (1922), Harbridge (1924), and Locket (1949).

Clinically, the fundus is pale and anaemic with narrow retinal arteries. The optic disc may show blurred margins (Whiting, 1929; Locket, 1949; Walsh, 1957; and others) or oedema (Whiting, 1929; Goulden, 1929; Barr, 1934; Wolff, 1935; Ballantyne, 1935; Locket, 1949, and others) which may be marked and may involve only the upper half of the disc (Ballantyne, 1935). There may be small superficial haemorrhages near the optic disc. The retinal veins may be congested. Later all these cases show optic atrophy (Hirschberg, 1881; Ziegler, 1887; Raehlmann, 1889; Görlitz, 1920; and many others), which may involve only the upper half of the disc (Uhthoff, 1922; Ballantyne, 1935). There may, however, be pronounced loss of vision without any significant fundus changes during the early stages (Locket, 1949; Müller, 1953; Walsh, 1957; and Hughes, 1958), though later optic atrophy is almost always seen.

Altitudinal hemianopia with loss of the lower visual fields has been seen by von Graefe (1860), Grout (1914), Pincus (1919), Terrien (1921), Uhthoff (1922), Collins (1929), Wolff (1935), Locket (1949), Hughes (1954, 1958), Comberg (1956), Scott (1957), Piper and Unger (1957), Ferreira and Parreira (1957), Gálvez Montes (1959), Harrington (1964b), and others. Less commonly it may involve the loss of the upper visual fields (Hughes, 1958). In these cases, the hemianopia is irregular and the line of demarcation is along the horizontal meridian. The preserved field shows a generalized depression (Hughes, 1958). There may be vertical hemianopia (Scott, 1957; Harrington, 1964b), bitemporal hemianopia (Harrington, 1964b), concentric contraction of fields (Grout, 1914; Goulden, 1929; Harrington, 1964b), or central scotoma (Grout, 1914; Barr, 1934). Scott (1957) described wide sectoral field defects in these cases which may produce irregular hemianopias, either vertical or horizontal.

The pathological lesions described in these cases are not definite. Zeigler (1887), Seese (1914), and Görlitz (1920) reported them 22, 5, and 11 days respectively after the onset of blindness. They found degeneration of ganglion cells, cytoid bodies in the nerve fibre layer, oedema of the retina, and fatty degeneration in the optic nerve. Gōrlitz (1920) found the last change in the optic nerve situated behind the lamina cribrosa.

The pathogenesis of post-haemorrhagic amaurosis, particularly that of the altitudinal and other field defects, has been the subject of much controversy. It has been considered to be due probably to primary ischaemia of the retina (Ziegler, 1889; Collins, 1929; Langdon, 1933; Cordes, 1958), focal anoxia of the retina (Pears and Pickering, 1960), vasospasm of the retinal arteries (Hartmann and Parfonry, 1934; Wolff, 1935), lack of oxygen similar to quinine amblyopia (Wolff, 1935), central retinal vein thrombosis (Cox, 1944), or ischaemic fatty degeneration of the optic nerve (Westhoff and Ziegler, 1899). Its prevalence after repeated haemorrhages and the lapse of time between the haemorrhage and the visual disorders suggest the possible role of some haemoclastic shock, anaphylactic crisis, or toxaemia due to profound haemolysis or other unknown causes (Holden, 1899; Groenouw, 1904; Pincus, 1919; Terrien, 1921; Terson, 1922; Kummel, 1932; Rønne, 1932; Duggan, 1943; and others). Duggan (1943) thought the toxin was adrenaline. Riser, Felgines, Gayral, Géraud, and Ribaut (1951) suggested that auto-intoxication was added to ischaemia to cause visual loss. Terrien (1921) thought the optic atrophy was due to the combined effect of haemorrhage and toxaemia. Other workers have suggested haemorrhage into the optic nerve sheath (von Graefe, 1860), oedema and multiple haemorrhages in the nerve (Leber, 1877), thrombotic foci causing degeneration and diffuse retinal oedema (Görlitz, 1920), endothelial damage due to blood loss and thrombosis on damaged endothelium (Uhthoff, 1922), endarteritis fibrosa (Raehlmann, 1889), thrombosis of the central retinal artery (Theobald, 1899), retrobulbar neuritis (Hoffman, 1899), a lesion in the optic nerve just behind the lamina cribrosa (Pears and Pickering, 1960), exudation into the sheath of the optic nerve with associated cerebral oedema sufficient to produce compression of the vascular supply of the optic nerve and retina (Fisher, 1929), changed consistency of the blood (Wilbrand and Saenger, 1906), and hypoproteinaemia leading to oedema of the optic nerve and vascular compression (Locket, 1949).

Inferior altitudinal hemianopia, according to Wolff (1935), is due to the effect of gravity, the lower part of the retina receiving more blood than the upper part after severe haemorrhage. There is accompanying atrophy of the upper half of the discs and diminution in calibre of the upper retinal arteries. Wolff postulated that the oedema of the optic disc in these cases was due to Starling's phenomenon, wherein the cutting off of the blood supply injures the endothelium of the capillaries, so that when the blood pressure is restored in them, an excessive amount of fluid is allowed to pass through the walls and produces oedema. Hughes (1958) commented that, in altitudinal hemianopia, the horizontal line of demarcation would suggest a retinal origin. In one example he observed the fundus during the episode and found the retinal vessels to be normal. In this case the horizontal line of demarcation did not exactly follow the horizontal meridian and it seemed probable that the lesion lay in the optic nerve. He reported another similar case. Harrington (1964b) thought it to be due to ischaemia of the anterior part of the optic nerve secondary to extreme hypotension or to stenosis or embolism of the optic nerve branches from the ophthalmic artery. Walsh (1957) postulated thrombosis affecting the visual cortex or optic radiation due to a fall in blood pressure in cases in which the fundus was normal.

The possibility that in some cases the visual disturbances, especially total blindness, are due to occlusion of the central retinal artery cannot be ruled out. In these, however, a normal fundus and normal retinal vessels have frequently been reported, and one can hardly find a case report showing a fundus picture of classical central retinal artery occlusion. The presence of an extreme arterial hypotension has been reported in these cases. The altitudinal hemianopia seen frequently in these cases has, I feel, the same pathogenesis as that discussed above (p. 302), *i.e.* it is due to involvement of the choroidal circulation to one half of the disc and choroid (Figs 6*a* and 7). In some cases, this could be the result of thrombosis affecting the posterior ciliary vessels because of extreme arterial hypotension. *The presence of an isolated oedema of the optic disc without any retinal oedema can be produced only by occlusion of the ciliary supply to the disc* (Hayreh, 1969). The presence of vertical hemianopia in these cases can sometimes be explained on the same basis as altitudinal hemianopia, where the main posterior ciliary artery supplies the temporal and nasal halves (Figs 1, 2, 3, and 5) instead of the superior and inferior halves (Figs 6*a* and 7). Since smaller subdivisions of the posterior ciliary arteries supply small sectors of the disc, their individual involvement would lead to a sectoral defect, as discussed above.

Conclusions

(1) The posterior ciliary arteries have a segmental supply in the choroid and optic disc. The main posterior ciliary artery usually supplies half of the choroid and optic disc, more commonly the nasal or temporal half, less often the superior or inferior half. The smaller short posterior ciliary arteries supply smaller sectors which may be quadrantic or smaller. The segments are usually sharply demarcated.

(2) The main source of blood supply to the optic disc comes from the ciliary circulation. The prelaminar part of the disc is supplied by the peripapillary choroid.

(3) The recurrent pial branches from the peripapillary choroidal vessels and the circle of Zinn and Haller contribute to the peripheral centripetal vascular system of the retrobulbar part of the optic nerve. The axial centrifugal vascular system in this part of the nerve is usually formed by the central retinal artery.

(4) Occlusion of one of the posterior ciliary arteries or one of its smaller subdivisions through any cause would involve a sector of the lamina cribrosa, the prelaminar part of the optic disc, and the retrolaminar part of the disc. This would lead to a nerve fibre bundle defect, the size and shape of the defect depending upon the artery involved.

(5) A complete occlusion of the posterior ciliary artery produces ischaemic optic neuropathy, while an incomplete occlusion, *e.g.* in arteriosclerosis, produces glaucomatous changes in the optic disc and nerve.

(6) Visual field defects in glaucoma are vasogenic in origin through involvement of the nerve fibres in the optic disc and nerve secondary to choroidal vascular obliteration.

(7) Glaucoma may be defined as a disease in which the normal balance between the intraocular pressure and the blood pressure in the choroidal vessels supplying the optic disc and the retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and retrolaminar part of the optic nerve, which in turn produces the visual field defects and the optic disc and optic nerve changes.

(8) Low-tension glaucoma is a type of glaucoma in which, instead of raised intraocular pressure, there is a fall in blood pressure in the ciliary vessels leading to the same end-results as in glaucoma.

(9) Prechiasmal altitudinal hemianopia may be produced by occlusion of one of the main posterior ciliary arteries which supplies the upper or lower half of the choroid and optic disc.

(10) Prechiasmal vertical hemianopia may be produced by occlusion of one of the main posterior ciliary arteries which supplies the nasal or temporal half of the choroid and optic disc.

(11) Quadrantic or sectoral field defects may be produced by occlusion of one of the smaller subdivisions of the posterior ciliary artery. The size and shape of the defect depends upon the artery involved.

(12) Peripheral contraction of the visual fields is frequently produced by the involvement of the pial vessels of the optic nerve which constitute its centripetal peripheral vascular system. The pial vessels of choroidal origin in the retrolaminar part of the optic nerve may be involved in glaucoma secondary to the involvement of the peripapillary choroid and this may result in peripheral contraction of the field in glaucoma.

(13) In post-haemorrhagic amaurosis, the visual disturbances and visual field defects, including altitudinal hemianopia, may frequently be due to the involvement of the ciliary blood supply to the optic disc and choroid. The type of defect depends upon the ciliary artery involved.

Summary

In the present study the choroidal vascular pattern and its contribution to the optic disc was studied in 24 eyes of monkeys by rapid serial fluorescence fundus angiography. This revealed a segmental supply by the posterior ciliary arteries in the choroid and optic disc. The size of the segment depended upon the size of the artery. The main posterior ciliary artery usually supplies half of the choroid and optic disc, which is more often the temporal or nasal half and less commonly the upper or lower half. The smaller arteries supply smaller sectors of these segments, which may be quadrantic.

The ciliary circulation has a very important role to play both in the pathogenesis of different types of visual field defects, most of which have so far remained ill-understood, *e.g.* nerve fibre bundle defects of different origins, visual field defects in glaucoma, altitudinal and vertical hemianopias of prechiasmal origin, quadrantic and sectoral defects, and in post-haemorrhagic amaurosis.

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Ischaemia in vein occlusions

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Paton, Rubinstein, and Smith (1964), Hayreh (1964), and Rabinowicz, Litman, and Michaelson (1968) suggest that the pathology in central vein occlusion is primarily an arterial ischaemia. If this in fact made a significant contribution to aetiology, then, in the presence of a unilateral vein occlusion, it would be reasonable to expect an ipsilateral ocular ischaemia. The purpose of this paper is to investigate the incidence and site of relative ocular ischaemia using a combined thermometric and angiographic approach.

Material and methods

Corneal and periorbital skin temperatures of 44 patients with vein occlusions (21 central and 23 branch veins) were measured with a bolometer (Mapstone, 1968a) over a period of up to 2 years from their first attendance at hospital.

In addition anterior segment angiograms were obtained from each patient using a Zeiss fundus camera and flash unit. 3 ml. 25 per cent. fluorescein were injected into an antecubital vein and photographs were taken at 5-second intervals for 90 seconds and again at 5- and 10-minute intervals.

Results

SURFACE TEMPERATURE

Of the 21 patients with central vein occlusions, all had a normal R-L temperature difference for medial forehead skin, whereas two had abnormal corneal temperature differences (normal = ±0·4°C. for cornea and ±0·6°C. for skin: Mapstone 1968c). Both of these had a rubeotic glaucoma with hyphaema. In one the latter was constant and the ipsilateral corneal temperature constantly greater as a result of the inflammation produced. In the other the cornea was significantly colder in the absence of hyphaema, but when blood was present it became hot (Fig. 1).

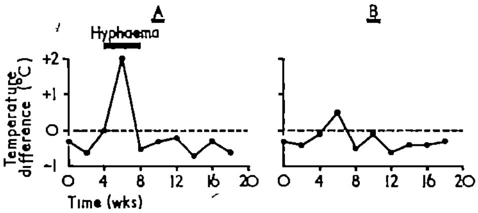

FIG. 1 *Temperature differences of patient with rubeotic glaucoma. Corneal differences are abnormally negative in the absence of hyphaema, the presence of blood producing an inflammatory reaction. Medial forehead differences are normal*

Of the 23 patients with branch vein occlusions, three had an ipsilateral cold cornea (Fig. 2, opposite), and one had initially the thermal pattern of a carotid stenosis which subsequently became normal (Fig. 3, opposite).

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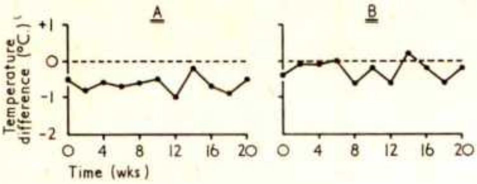


FIG. 2 *Temperature differences of patient with an ischaemic anterior segment. Corneal temperature differences are abnormally negative, medial forehead differences normal*

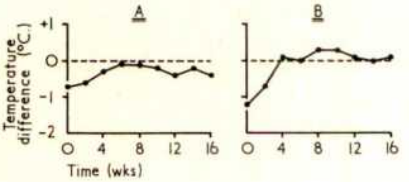


FIG. 3 *Temperature differences of patient with thermal pattern of carotid stenosis,* i.e. *abnormally negative corneal and medial forehead temperature differences. This pattern was present for the first* 2 *weeks only.*

ANTERIOR SEGMENT ANGIOGRAPHY

In eight of the 44 patients neovascularization was seen by slit-lamp examination. Fig. 4 illustrates the angiogram of one: (*a*) shows the fluorescein leak at 25 seconds and (*b*) the R-L difference of the same patient 5 minutes after injection. Five of the eight patients had rubeotic glaucoma and all had central vein occlusions. One had an ischaemic anterior segment (Fig. 1).

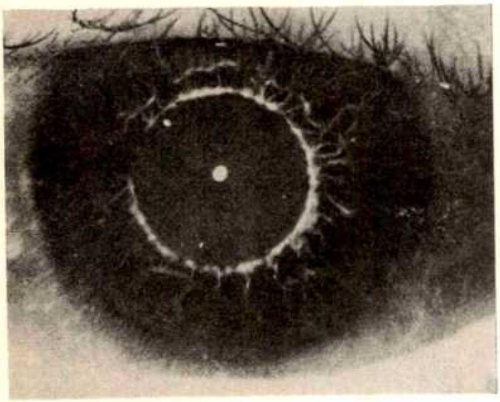
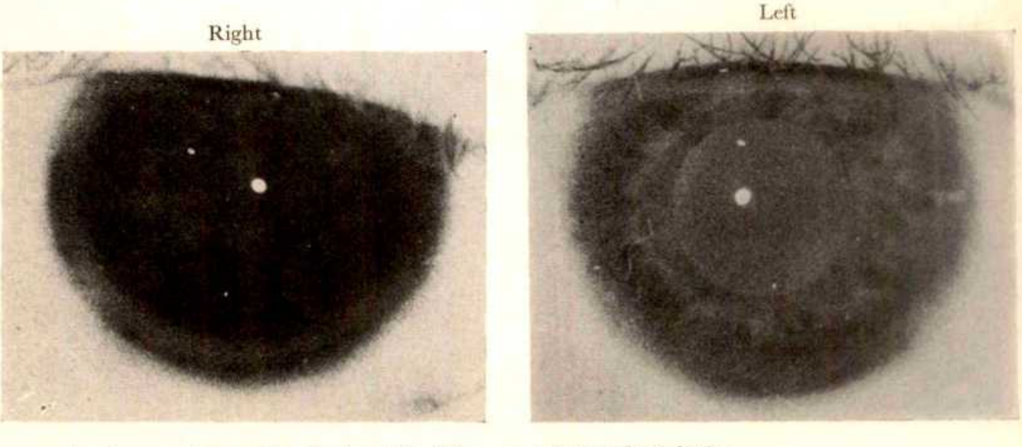


FIG. 4*a* *Anterior segment angiogram of patient with early rubeosis iridis* 25 *seconds after fluorescein injection*



Right

Left

FIG. 4*b* *Same patient as* (a), *showing R-L difference* 5 *minutes after injection.*

Of the remaining 36 patients, although no neovascularization was visible, three had abnormal angiograms (in that present experience of approximately 150 angiograms indicates no fluorescein leak in the normal iris apart from the delineation of vascular patterns, whereas these patients had an abnormal blush at the pupillary margin: Fig. 5). None had an ischaemic anterior segment, but all three had central vein occlusions.

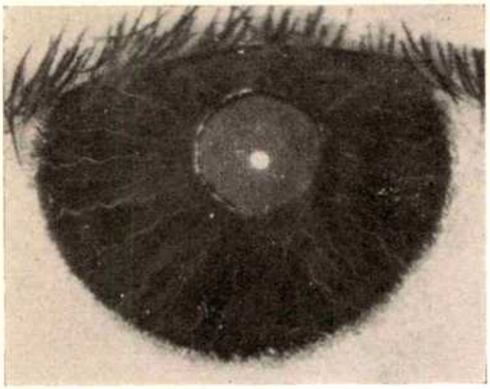


FIG. 5 *Angiogram of patient with normal slit-lamp appearances, showing fluorescein "blush" at pupillary margin 45 seconds after fluorescein injection*

Discussion

The probable site of a unilateral stenosis producing ischaemia can be inferred from surface temperature measurement, for the following reasons:

(1) A lesion of the carotid vascular tree at any site before the origin of the ciliary arteries will produce a cold cornea and patch of medial forehead skin.

(2) A cold cornea with normal skin temperatures is the result of a unilateral diminished ciliary artery supply or stenosis/destruction of vessels within the anterior uvea.

(3) A lesion of the central retinal artery or its branches will leave the surface thermal patterns unaffected.

There are fallacies in this method, *e.g.* the development of R-L anastomoses, but the conclusions are probably valid in 70 to 80 per cent. of patients with stenosing carotid lesions, and in a higher percentage still with anterior uveal ischaemia (Wood, 1964, 1965; Austin and Sajid, 1966; Mapstone, 1968a, b, c, d, e).

Incidence of ischaemia

The incidence of ischaemia due to carotid lesions in this group of patients is very different from that found by Smith (1954). Using an ophthalmodynamometer, he found presumptive evidence of carotid stenosis in 30 per cent. of a group of 73 patients. Of the 44 patients in the present group, one had transient evidence of a carotid lesion (Fig. 3) and four of an isolated anterior segment ischaemia.

Site of ischaemia

The ischaemia was situated in the carotid system proximal to the branching of the ciliaries from the ophthalmic artery in one patient (Fig. 3), and in the ciliaries or anterior uvea in four. Surface thermal patterns, however, cannot indicate the presence or absence of posterior segment ischaemia; presumptive evidence can nonetheless be obtained from anterior segment angiograms and the presence of anterior uveal neovascularization: in the five patients mentioned above with ischaemic anterior segments, one had rubeosis iridis, seven further patients had rubeosis, abnormal angiograms (Fig. 4), and normal thermal patterns, and three had an iris blush (and no diabetes—Cobb, 1968) but again normal thermal patterns. In eleven patients with neovascularization, therefore, one only had an anterior segment ischaemia, whilst in five with ischaemia one had new vessels. The inference is that anterior segment ischaemia and neovascularization are not causally related but rather that—as suggested by Smith (1954, 1955)—a vasoactive metabolite is released by the ischaemic retina and its anterior diffusion causes the vascular changes. Here, however, the retinal ischaemia is a consequence, and not a cause, of the vein occlusion.

In only five patients, therefore, is there evidence of relative extraretinal arterial ischaemia, and it is concluded that if ischaemia is a major causal factor of vein occlusions it must reside within the central retinal artery or its branches.

Summary

44 patients with vein occlusions were investigated using a combined angiographic and thermometric technique.

Five only had evidence of an extraretinal arterial ischaemia.

If ischaemia and vein occlusion are related, the arterial pathology lies within the central retinal artery or its branches.

I should like to thank the surgeons of St. Paul's Eye Hospital for access to their patients.

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Treatment of suppurative intraocular infections

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Suppurative intraocular infection is a devastating complication of intraocular surgery and penetrating wounds of the globe. Despite the advent of the corticosteroids and newer antibiotics, the prognosis remains very grave. Even with prompt treatment, useful vision is permanently lost in the majority of cases and frequently the globe has to be eviscerated. Fortunately during the last two decades the incidence of postoperative intraocular infections has decreased, mainly through improvements in surgical and aseptic techniques and the use of prophylactic antibiotics.

This paper describes a therapeutic regime which has been used in the treatment of twenty cases of suppurative intraocular infection. In no case did the infection lead to the loss of the globe.

Material and methods

Twenty cases of suppurative intraocular infection (Table I) arising from a variety of causes were treated as inpatients at the High Holborn Branch of Moorfields Eye Hospital from April, 1968, to November, 1969. Their ages ranged from 4 to 70 years. There were fourteen males and six females.

All twenty patients showed signs of intraocular suppuration from an exogenous source. The criteria for the diagnosis were based on clinical observations following a complete ocular examination and history, other possible causes of uveitis having been excluded. Nine cases were due to infected drainage blebs, seven were postoperative, and four followed penetrating wounds of the globe.

In the majority of cases the following regime was adopted:

(1) SUBCONJUNCTIVAL THERAPY

(*a*) *Immediate*

The conjunctival sac was anaesthetized with 4 per cent. cocaine and adrenaline drops. Two separate injections were given, one into the upper fornix and the other into the lower.

(*i*) One injection consisted of methylprednisolone acetate (Depomedrone) 40 mg. This ensures an adequate concentration of steroid in the anterior chamber for up to 5 weeks.

(*ii*) The other injection consisted of a "cocktail" of the following; gentamicin (Gentisin) 20 mg. (0·5 ml.), framycetin (Soframycin) 500 mg. (1 ml.), methicillin (Celbenin) 150 mg. (0·2 ml.), and mydricaine (atropine, adrenaline, and procaine) 0·3 ml. The methicillin was made up by dissolving 1 g. Celbenin used for intramuscular injection in 1·5 ml. of saline and using 0·2 ml. The total volume of the "cocktail" was 2 ml. As much as possible of this was injected beneath Tenon's capsule. It is important not to inject merely beneath loose conjunctiva.

(*b*) *Subsequent*

This consisted of a mixture of methicillin 150 mg., gentamicin 20 mg., and betamethasone (Betnasol) 4 mg. (1 ml.) given at 24- or 48-hourly intervals depending on the response to treatment and state of the conjunctiva.

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Table I *Survey of patients*

Case No.	*Age (yrs)*	*Sex*	*Presumed aetiology*		*Anterior chamber*	*Red reflex*	*Onset of response*
1	66	M	Infected drainage bleb	Trephine 11 yrs ago	Hypopyon 8 mm.	±	6th day
2	70	M		Anterior flap sclerotomy 4 yrs ago	Hypopyon 3 mm. Fibrinous exudate	—	2nd day
3	68	M		Trephine 15 yrs ago	Hypopyon 2 mm.	—	5th day
4	68	M		Scheie's operation 6 mths ago	Hypopyon 1 mm.	±	3rd day
5	53	M		Drainage operation 16 yrs ago	Hypopyon 1 mm.	—	Immediate
6	67	F		Trephine 1 yr ago	Hypopyon 2 mm.	±	Immediate
7	60	F		Lens extraction resulting in "bleb" 2 yrs ago	Cells+++	+	2nd day
8	63	M		Iridencleisis 8 yrs ago	Hypopyon 1 mm.	±	5th day
9	60	M		Anterior flap sclerotomy 10 yrs ago	Cells +++ Fibrinous exudate	—	2nd day
10	38	F	Postoperative infection	Lens extraction Hypopyon on 3rd postoperative day	Hypopyon 2 mm.	—	Immediate
11	67	M		Lens extraction Hypopyon on 2nd postoperative day	Hypopyon 1 mm.	+	Immediate
12	32	M		Lens extraction and vitrectomy Hypopyon on 2nd postoperative day	Hypopyon 3 mm.	+	Immediate
13	5	M		Irido-capsulectomy Hypopyon on 2nd postoperative day	Hypopyon 3 mm.	—	Immediate
14	53	F		Retinal detachment operation with release of sub-retinal fluid Exudate on 2nd postoperaative day	Dense fibrinous exudate filling anterior chamber	+	2nd day
15	68	M		Retinal detachment operation with release of sub-retinal fluid and injection of intravitreal saline Exudate on 2nd postoperative day	Dense fibrinous exudate	—	2nd day
16	56	M		Re-suturing of corneal graft Hypopyon on 5th postoperative day	Hypopyon 2 mm.	—	Immediate
17	4	F	Penetrating injury	Penetrating corneal wound neglected for 2 days Iris prolapse	Dense fibrinous exudate	—	Immediate
18	55	M		Metallic intraocular foreign body removed with magnet Hypopyon on 3rd postoperative day	Hypopyon 2 mm.	+	Immediate
19	4	F		Penetrating corneal wound	Hypopyon 2 mm.	±	2nd day
20	13	M		Penetrating corneal wound	Hypopyon 2 mm.	—	5th day

(2) SYSTEMIC THERAPY

(i) Antibiotics

Cloxacillin (Orbenin) 2 g. 6-hourly orally.

(ii) Corticosteroids

Prednisolone 40 mg. daily in divided doses.

(iii) Acetazolamide (Diamox)

This was necessary in three cases in which secondary glaucoma occurred.

(3) TOPICAL THERAPY

(i) Antibiotics

Gentamicin drops hourly and ointment at night.

(ii) Corticosteroids

Predsol or dexamethasone drops hourly.

(iii) Mydriatics

Atropine 1 per cent. 6-hourly.

The sensitivity of pathogenic organisms to the various antibiotics is shown in Table II.

Table II *Antibiotics*

Antibiotics		*Methicillin*	*Cloxacillin*	*Framycetin*	*Gentamicin*
Sensitivity of organisms	*Staph. aureus*	++	++	++	+++
	Penicillin-resistant *Staph. aureus*	+++	+++		+++
	Strept. pyogenes	++	++	±	±
	Pneumococcus	++	++	+++	±
	Proteus vulgaris			++	+++
	Ps. pyocyanea			++	+++
Dose	Subconjunctival	150 mg.		100–500 mg.	20 mg.
	Systemic	2 g. 6-hrly intramuscular or intravenous	2 g. 6-hrly oral		
Systemic side-effects		Allergy and hypersensitivity Reversible bone marrow depression (rare) Albuminuria and haematuria	Allergy and hypersensitivity Mild gastro-intestinal upsets		

Results

The clinical response to therapy was graded as good, fair, and poor. The basic criterion for the grading was the comparison of the visual acuity before the onset of infection and the visual acuity after the completion of therapy. The response was considered good when there was no deterioration in the visual acuity, fair when the visual acuity fell by not more than two lines on the Snellen test type or from counting fingers to hand movements, and poor when there was a more considerable loss of visual acuity.

Of the twenty patients treated, thirteen responded well with no loss in visual acuity (Table III, overleaf), two (Cases 1 and 16) showed a fair response, and in the remaining five the response was poor (Cases 2, 3, 15, 17, and 20). The results in Case 3 are shown in the Figure.

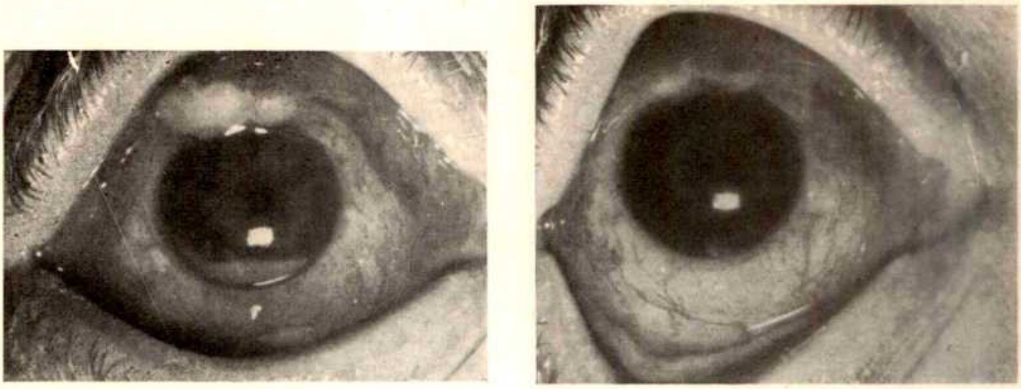

FIGURE *Case 3. Before and after treatment*

In Case 1 the visual acuity fell from 6/9 to 6/18 because of the development of lens opacities. In Case 16 a fall from counting fingers to hand movements and in Case 3 from counting fingers to perception of light was due to the development of a pupillary membrane. In Case 2 there was a dramatic fall from 6/9 to counting fingers although the eye was quiet with a clear vitreous because of the development of macular "oedema". In Case 15 the eye became blind through ischaemia resulting from an encircling procedure as well as vitreous organization. The poor result in Case 17 was due to the formation of corneal and lenticular opacities and in Care 20 to vitreous organization.

The speed of response to treatment varied considerably from case to case. Improvement was immediate in nine cases, but the other eleven showed a deterioration lasting from 2 to 6 days (Case 1) before improving. No case relapsed after an improvement.

Discussion

The treatment of suppurative intraocular infection is relatively disappointing because of the general destruction of the intraocular tissues by the inflammatory process set up by the invading organisms. Treatment must be prompt and vigorous to be of any effect, as with each hour that passes further irreversible damage is being done to the globe.

The regime described above has been used, with minor modifications, in treatment of twenty such cases. The aim of the treatment is to overcome the causative organism with antibiotics and to reduce the destructive inflammatory process to a minimum by the use of corticosteroids. Steroid therapy will not interfere with the control of the infection provided that the infecting organisms are sensitive to the antibiotics, and the dose is adequate to penetrate the intraocular tissues. The cardinal prerequisite to successful therapy is the selection of the proper drugs.

Theoretically, the infecting organisms should be identified and their sensitivities to various antibiotics determined. Unfortunately, conjunctival cultures are seldom helpful and even cultures taken from the anterior chamber in cases of overwhelming infections may

Table III *Visual Acuity*

Case No.	*Before infection*	*At onset of treatment*	*After treatment*	*Result*
1	6/9	HM	6/18 Lens opacities	Fair
2	6/9	HM	CF Macular "oedema"	Poor
3	CF Cataract	PL	PL Cataract Pupillary membrane	Poor (see Figure)
4	6/18 Cataract	CF	6/18	Good
5	HM Cataract Corneal opacity	HM	HM	Good
6	6/9	HM	6/9	Good
7	6/6	6/9	6/6	Good
8	2/60 Gross field loss	CF	2/60	Good
9	CF Cataract	PL	CF	Good
10	6/60 Cataract	HM	6/9	Good
11	6/36 Cataract	PL	6/6	Good
12	PL Vitreous haemorrhage	PL	PL	Good
13	HM Capsular remnants	PL	HM	Good
14	6/12 Retinal detachment	HM	6/12	Good
15	HM Retinal detachment	No PL	No PL Ocular ischaemia Vitreous organization	Poor
16	CF Corneal graft	HM	HM Pupillary membrane	Fair
17	6/6	HM	PL Lens and corneal opacities	Poor
18	6/5	?	6/5	Good
19	6/6	?	6/6	Good
20	?	PL	PL Vitreous organization	Poor

CF = counting fingers
HM = hand movements
PL = perception of light

be negative. Even when they are positive they may not disclose the causative organism. In all but one of these patients (Case 8) conjunctival cultures were of no help and treatment was empirical.

The organism most commonly responsible for postoperative infection is *Staph. aureus*, which may be penicillin resistant. Gram-negative organisms, such as *Ps. pyocyanea* and *Proteus vulgaris*, may also occasionally be responsible. Other Gram-positive cocci, such as *Strept. pyogenes* and the *Pneumococcus*, may be responsible for infections after penetrating injuries.

The antibiotics used in the treatment of bacterial intraocular infections should be capable of covering all eventualities. If a therapeutic level of drugs is to be reached promptly and in an adequate concentration, it is necessary to combine subconjunctival with systemic and topical administration. Intracameral administration is not recommended as it gives very disappointing results. It was used only in Case 17 as a last resort.

It is important that the antibiotics administered subconjunctivally should differ from those given systemically in order to allow a greater opportunity for the pathogen to be susceptible to at least one of them.

Methicillin is the antibiotic of choice in the treatment of penicillin resistant *Staphylococci*, as it is immune to penicillinase and highly bactericidal. In this regime it was administered only subconjunctivally.

Gentamicin is a new bactericidal antibiotic which is water-soluble and well tolerated when injected subconjunctivally. It is highly active against an exceptionally wide range of bacteria, including penicillin-sensitive and resistant *Staphylococci*, group A beta-haemolytic *Streptococci*, *Proteus vulgaris*, and *Ps. pyocyanea*. It plays a very important part in the treatment of intraocular infection and was administered both subconjunctivally and topically.

Framycetin is soluble and well tolerated when given subconjunctivally. It has a wide spectrum which includes both *Staph. aureus* and *Ps. pyocyanea*. It is not, however, effective against penicillin resistant *Staphylococci* and does not play a major role in the treatment of intraocular infection.

Cloxacillin was the only antibiotic used systemically. It has the same spectrum as methicillin and has the added advantage that it may be administered orally, though it may cause nausea and vomiting when given in high doses. This happened in two of our patients and the drug had to be discontinued. It cannot be injected subconjunctivally as it causes a severe reaction. It should not be used in penicillin-sensitive patients.

In order that the inflammatory damage may be reduced to a minimum while the antibiotics are gaining control of the infection, it is essential that corticosteroids be administered simultaneously.

Prednisolone was used systemically, methylprednisolone and betamethasone subconjunctivally, and Predsol and dexamethasone topically.

Mydriatics should be administered both subconjunctivally and topically to combat the formation of posterior synechiae and to relieve pain due to pupillary and ciliary spasm.

The duration of treatment varies according to the response. It is usually unnecessary to give more than four subconjunctival injections. Systemic steroid therapy can usually be reduced after 5 days and stopped altogether after 10. Topical therapy with gentamicin and dexamethasone should be continued for several weeks until the anterior chamber is completely quiet. It is important to note that it may sometimes take several days for the patient to show a response to treatment. The eye should not be given up as lost until it has had the benefit of at least 7 days of intensive therapy.

Summary

A therapeutic regime consisting of subconjunctival, systemic, and topical administration of antibiotics and corticosteroids in the treatment of twenty cases of suppurative intraocular infection is described. The response was considered to have been good in thirteen cases, fair in two, and poor in five. The rationale of the treatment is discussed.

I am much indebted to the consultant staff of the High Holborn Branch of Moorfields Eye Hospital for permission to describe their cases, to the house surgeons for all their help, and in particular to Mr. Barrie Jay for his most helpful advice and encouragement.

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Inheritance of Duane's syndrome

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The retraction syndrome described by Duane in 1905 comprises complete or less often partial absence of abduction, with retraction of the affected eye into the orbit and narrowing of the palpebral fissure on adduction. There is often an upshoot or downshoot of the globe on adduction. On attempted abduction there is usually slight protrusion of the globe with widening of the palpebral aperture.

A familial incidence has been noted in about 10 per cent. of the cases reported in the literature (Duke-Elder, 1964), although in most reports no adequate family investigation appears to have been made.

Familial cases of Duane's syndrome have been reported by many authors during the past 100 years.†

Also, evidence for "formes frustes" of Duanes' syndrome in other family members in the form of pareses of oculomotor muscles other than the lateral rectus or of slight narrowing of the palpebral fissure on adduction, has been reported by François and de Vos (1958) and by Orlowski, Krych, and Michniowska-Leonowicz (1961).

Most of the above observations have been confined to single sibships, or to two and occasionally three generations. Duane's syndrome has occurred as an isolated phenomenon in each of these reports, apart from those of Mein (1968) and Kirkham (1969a) where perceptive deafness was a feature, and Waardenburg (1963) where the Klippel-Feil anomaly was seen in a girl and in her paternal aunt.

The Klippel-Feil anomaly consists of a variety of bony deformities of the cervical spine, usually involving fusion, which appears clinically as a short neck with a limited range of movements of the head and neck and a low posterior hairline.

Present investigations

This paper attempts to elucidate the nature of the genetic factors responsible for the inheritance of Duane's syndrome and its relationship to perceptive deafness and to the Klippel-Feil anomaly.

Between the years 1949 and 1968, a total of 149,000 new patients with strabismus was seen in the Orthoptic Clinics of the United Sheffield Hospitals; of these only 126 (0·84 per cent.) had Duane's syndrome. This accords well with the experience of White and Brown (1939), who found that twelve (1·1 per cent.) of their 1,062 patients with strabismus had Duane's syndrome.

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† Harlan, 1885; Günsburg, 1889, Turk, 1896, 1899; Wolff, 1900; Varese, 1901; Best, 1903; Kraus, 1905; Endelman, 1911; Peters, 1921; Waardenburg, 1923, 1932, 1953, 1963; Gifford, 1926; Zentmayer, 1935, Lodberg, 1937; Malbrán, 1949, Schlossman and Priestley, 1952; Bohringer, 1952; Weekers and Daenen, 1955; Gundersen and Zeavin, 1956; Gedda and Magistretti, 1956; François and De Vos, 1958; Bekenn, 1961; Dias Alves, 1961; Pintucci and Di Tizio, 1961, Goldfarb and Gannon, 1964, Kanbayashi, Ichikawa, Tani, Maki, Taji, and Kaino, 1967, Mein, 1968; Kirkham, 1969a.

The clinical picture in this condition is known to be variable. Lyle and Wybar (1967) subdivided such patients into three groups according to the degree of involvement of abduction or adduction; for the present study this was not considered important and would have been difficult in view of the many variations seen.

The 126 patients in this series comprised 82 females (65 per cent.) and 44 males (35 per cent.). In the male patients, the syndrome affected the right side in eight, and the left side in twenty-six, and was bilateral in ten. In the female patients the right side was involved in twenty, and left side in fifty, and both sides in twelve. Thus, in all, the right side was involved in 22 per cent., the left side in 60 per cent., and both sides in 18 per cent. of cases

Detailed family histories were obtained from 94 of these patients who were traced and re-examined. Wherever the possibility of strabismus or deafness existed in a relative, ophthalmic or audiological examinations were arranged. In many of the families there were cases of concomitant strabismus and otosclerosis, but the investigations of others revealed patients with Duane's syndrome or perceptive deafness.

A further eighteen patients replied to a questionnaire, denying the presence of deafness or cervical spine anomalies, and of squint, deafness, or cervical spine anomalies in relatives. The clinical records of the remaining fourteen patients made no reference to the presence (or absence) of deafness or spinal anomalies.

Of the 112 patients for whom clinical information was complete, twelve had perceptive deafness and five had the Klippel-Feil anomaly. Only two patients demonstrated the full triad of Klippel-Feil anomaly, Duane's syndrome, and perceptive deafness.

Figures 1, 2, and 3 show the pedigrees of the index patients who were themselves deaf or had the Klippel-Feil anomaly, or in which other members of the family were affected by Duane's syndrome or perceptive deafness. In one family a possible instance of the Klippel-Feil anomaly occurred in a female infant who died soon after birth; no *post mortem* examination was performed. The pedigree of a family affected through five generations with perceptive deafness in which two patients had Duane's syndrome has been reported elsewhere (Kirkham 1969a) and is not included here.

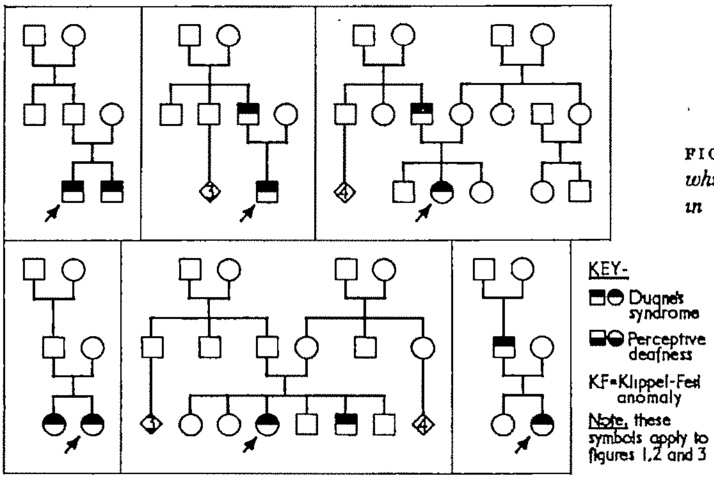

FIG. 1 *Pedigrees of families in which Duane's syndrome occurred in isolation*

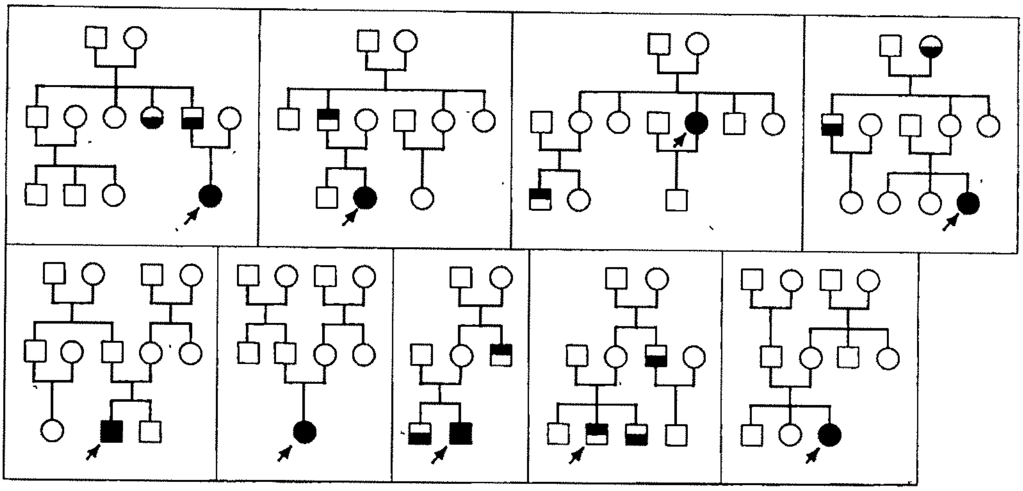

FIG. 2 *Pedigrees of families in which Duane's syndrome occurred with perceptive deafness*

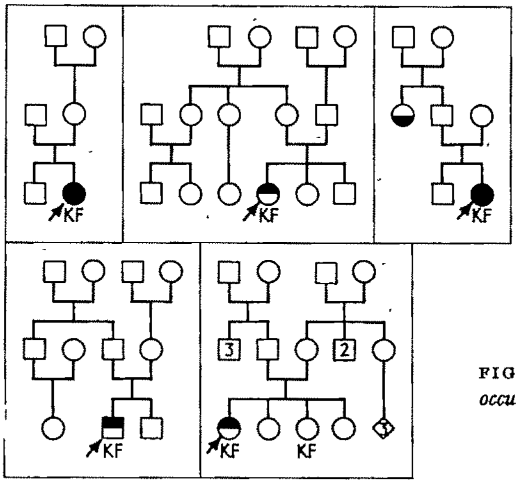

FIG. 3 *Pedigrees of families in which Duane's syndrome occurred in association with the Klippel-Feil anomaly*

Discussion

Isolated instances of Duane's syndrome with deafness or the Klippel-Feil anomaly are not unknown. Bielschowsky (1939) described a congenitally deaf-mute girl with bilateral Duane's syndrome, and Mein (1968) mentioned two cases of deafness in her series of 77 patients with Duane's syndrome. In a review of visual defects in deaf children, Stockwell (1952) noted that one female showed absence of the lateral rectus muscles, possibly a case of Duane's syndrome.

Single cases of Duane's syndrome associated with the Klippel-Feil anomaly have been reported by Mau (1924), Magnus (1944), Casellato and Meucci (1957), and Mein (1968). The male patient described by Baumann (1932) who could not turn either eye outwards possibly belongs to this category, as do the female patient of Thomson (1937) with an lateral rectus palsy and the girl described by Latto (1942) with the Klippel-Feil anomaly whose lateral ocular movements were said to be limited.

The association of profound childhood deafness with the Klippel-Feil anomaly is well established; Whetnall and Fry (1964) described three female patients, one of whom had defective vision (? Duane's syndrome). Fraser (1964) saw nineteen cases of the Klippel-

Feil anomaly in profoundly deaf children, and other similar cases were reported by Mitchell (1934), Bizarro (1938), Schwarze (1941), Erskine (1946), Bardadin and Siedlanowska (1955), Witzel (1958), and Cohney (1963).

A girl with the Klippel-Feil anomaly, Duane's syndrome, and congenital deafness was reported by Wildervanck (1952) and the same triad of signs in two other girls was documented by Waardenburg (1953). The syndrome was given the title cervico-oculo-facial dysmorphia by Franceschetti and Klein (1954) and by Pintucci and di Tizio (1961) who reported further cases. Wildervanck (1960) gave a detailed report of a similar girl who had, in addition, an epibulbar dermoid, and described further incomplete cases of the syndrome which he preferred to call the cervico-oculo-acusticus syndrome. The name "Wildervanck's syndrome" was suggested by Everberg, Ratjen, and Sorensen (1963) who described radiological abnormalities of the inner ear in a male patient with the syndrome. Further examples of the full syndrome have been described by Bintliff (1965), Wildervanck, Hoeksema, and Penning (1966), Franceschetti, Klein, Brocher, and Ammann (1966), Fraser and MacGillivray (1968), McLay and Maran (1969), and Kirkham (1969b.).

It is obvious from this review of the literature that a definite relationship exists between some cases of Duane's syndrome, perceptive deafness, and the Klippel-Feil anomaly.

Instances of deafness, often congenital, were discovered in relatives of the patients described by Bielschowsky (1939), Franceschetti and Klein (1954), Wildervanck (1960), Wildervanck and others (1966), Franceschetti and others (1966), and Kirkham (1969a). In addition, the brother of the patient described by Franceschetti and others (1966) was said to have had similar deformities of the neck and mouth which resulted in neonatal death. One relative of a patient described by Fraser and MacGillivray (1968) had a short neck and another a speech defect (? profound deafness). Considering these reports, together with the familial cases of Duane's syndrome mentioned earlier, it is clear that the relationship between Duane's syndrome, perceptive deafness, and the Klippel-Feil anomaly has a genetic basis.

Wildervanck (1952, 1960) at first considered that the combination of these signs was fortuitous and ascribed the syndrome to the status dysraphicus, but later (1963) concluded that the syndrome was transmitted as a recessive trait. Wildervanck and others (1966) saw evidence of the status dysraphicus ("short necks", anencephaly, rachischisis) and of deafness among the relatives of their patients with the cervico-oculo-acusticus syndrome, and considered a multi-factorial inheritance to be the most likely explanation. Franceschetti and others (1966), in discussing their familial observation, considered that the triad was inherited as an irregular dominant character with variable expressivity of the responsible pleiotropic gene. Discussing the inheritance of Duane's syndrome in isolation, Waardenburg (1963) expressed the opinion that an irregular dominant gene effect was responsible. Fraser and MacGillivray (1968) detected chromosomal damage in one of their patients, a girl showing mental deficiency in addition to the full syndrome.

In the present series of 112 patients with Duane's syndrome, twelve (10·7 per cent.) had perceptive deafness and five (4·4 per cent.) had the Klippel-Feil anomaly. The families of several of these patients included other instances of Duane's syndrome or perceptive deafness, and in one family a female sibling who died in infancy was said to have shown multiple congenital deformities, including a neck abnormality.

Interpreting these findings in association with those in the literature, it seems reasonable to suggest that Duane's syndrome, the Klippel-Feil anomaly, and perceptive deafness are inherited as a single gene trait which is manifest in the heterozygote. The gene is incompletely penetrant and exhibits variable expressivity; thus the clinical picture is that of a gene with pleiotropic effects inherited in an irregularly dominant manner. It is further suggested that the abnormal gene is partly sex-limited, acting on a polygenic background which is modified by sex in such a way that females are more susceptible or males are more resistant to the action of the gene. It is also possible that unknown environmental factors are of importance in modifying the expression of the gene.

In the large groups of isolated cases of Duane's syndrome, it is possible that some are not genetically determined but are the result of teratogenic agents to which the mother was exposed during pregnancy. Although in this series it has been ascertained that none of the mothers was diabetic and that there was no history of drug-taking or exposure to radiation and no history of rubella or other infections during pregnancy, this does not exclude the possibility of other unknown teratogenic agents.

Patients with Duane's syndrome in whom there was a history of the mother's having taken thalidomide during pregnancy have been described by Papst (1963) and Cullen (1967); in these patients abnormalities of the external ear were frequent. A series of five children with congenital ear deformities and deafness of a conductive nature due to atresia of the external auditory meatus was described by Livingstone and Delahanty (1968). These patients showed abnormal ocular movements indistinguishable from Duane's syndrome combined with weakness of the facial muscles resembling the Moebius syndrome; it is of interest that one of these patients showed the Klippel-Feil anomaly. The clinical features in these patients are so characteristic as to form a distinct syndrome; that thalidomide is not the only cause of this "toxic" Duane's syndrome is shown by an identical case reported by Warrington (1897). It is interesting that such environmental factors can act *in utero* to produce abnormal ocular movements indistinguishable from Duane's syndrome.

Summary

The literature relating to Duane's syndrome, perceptive deafness, and the Klippel-Feil anomaly is reviewed.

A series of 126 patients showing Duane's syndrome was studied and instances of perceptive deafness and the Klippel-Feil anomaly were found amongst these patients and their relatives.

It is concluded that the triad of Duane's syndrome, the Klippel-Feil anomaly, and perceptive deafness is inherited as a dominant condition with variable penetrance and expression. The gene is partially sex-limited and unknown environmental factors are possibly important in modifying its effect.

I wish to thank the Consultant Ophthalmologists of the United Sheffield Hospitals for allowing me to review their patients.

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Syndrome of "Crocodile Tears"

Pharmacological study of a bilateral case

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Pliny the Elder, whose writings are consistently more notable for their dramatic interest than for their scientific accuracy, related the story of the crocodile's hypocritical tears. After devouring the body of a victim, the reptile supposedly shed many tears over the head, before eating that also. Bogorad (1928) and Kaminsky (1929) applied the name "crocodile tears" to the syndrome of excessive lacrimation while eating. The more prosaic term for the syndrome, "paroxysmal lacrimation", is deservedly less popular.

Although relatively uncommon, the crocodile tears syndrome is of considerable interest. Most cases are acquired and unilateral and usually follow a Bell's palsy affecting the same side. Normally, the facial nerve contains fibres which are secretomotor for the submandibular salivary glands, as well as secretory fibres to the lacrimal gland. Anatomical features are discussed in detail by Savin (1939). The generally accepted explanation of the pathogenesis of crocodile tears (Walsh, 1957) is that, during recovery from Bell's palsy, regenerating salivary fibres in the facial nerve become misdirected and innervate the lacrimal gland. Stimuli such as the taste or smell of food, which normally would excite a flow of saliva, may then produce a simultaneous flow of tears on the same side as the original Bell's palsy. Chorobski (1951), in his extensive review of the syndrome, suggested that paroxysmal lacrimation was due, not to anomalous re-innervation of the lacrimal gland, but to ephaptic cross-stimulation of demyelinated but otherwise intact lacrimal fibres by efferent impulses in the salivary secretomotor fibres of the facial nerve. However, this hypothesis is not supported by Chorobski's own observation that, in cases of paroxysmal lacrimation, spontaneous emotional lacrimation is usually lost.

Crocodile tears have also been described as a congenital abnormality. Lutman (1947) discussed three patients with congenital paroxysmal lacrimation and paralysis of the lateral rectus muscle of the eye. In two of these cases both lesions were bilateral, and in the third both anomalies were unilateral, affecting the same eye. It was suggested that a lesion in the pons involved the abducent nucleus together with either the superior salivatory nucleus or the genu internum of the facial nerve as it loops around the abducent nucleus.

The present communication describes an unusual case of bilateral crocodile tears in which the lesion was acquired and followed a unilateral Bell's palsy. The patient was followed over several months and the effects of various drugs on lacrimation were studied. These studies may be helpful in the management of this sometimes very distressing syndrome.

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Case report

A 26-year-old Nigerian science graduate had sustained a fairly severe right Bell's palsy 10 years previously. This improved considerably, but 2 years later he had a recurrence on the same side, which also improved steadily, and thereafter from time to time he experienced intermittent flickering in the muscles of the right side of the face. One year before presentation he noticed that his right eye became moist when he was chewing. This became increasingly troublesome so that eventually tears overflowed from his right eye during most meals. His left eye then began to water during meals and within a few months the condition became, in his opinion, symmetrical. Lacrimation occurred every day and was more copious with highly spiced foods. Tears ran freely down his cheeks and became a social embarrassment. There was no history of a left facial weakness. Physical examination showed no abnormality other than mild weakness of the lower part of the right side of the face when grimacing. His eyes, eyelids, and optic fundi were normal and the lacrimal ducts were patent.

Observations

Tear production was measured by a modification of the blotting paper test of Schirmer (1903). Strips of Whatman No. 52 filter paper, 0·5 × 3·5 cm., were weighed and inserted into the lower conjunctival fornix of each eye, being folded at right angles over the ciliary border of the lid and left in position for 5 minutes. During this period the patient chewed three Whatman No. 1 filter papers previously dipped in a 2·5 per cent. solution of citric acid and air-dried. In this way the patient received a reproducible stimulus from both taste and mastication. After 5 minutes the conjunctival filter papers were reweighed and the tear output expressed in mg.

Control observations were made in six healthy young men using the same standard taste stimulus.

Serial observations of tear output were made over a period of 8 months and the effects of various local and systemic drug treatments were assessed. These observations are summarized in the Table and in the Figure (overleaf).

Comment

The reproducibility of readings which are closely related in time and where effects of treatment are not in question (*e.g.* those for the left eye on 6.2.69 and 14.2.69) suggests that this is a reasonably accurate method of measuring lacrimal secretion. When the control observations alone are considered, it is seen that the initial tear output was approximately twice the mean value for normal subjects. There was an initial inequality between the outputs of the two eyes: the patient was unaware of this. Furthermore, the serial observations show that, over several months, the greater tear output was sometimes from one eye and sometimes from the other: this did not correlate with alterations in symptoms.

The total tear output is seen to fall and later to rise, only to decrease once more, during the period of observation. The patient noticed a fluctuation in his symptoms; sometimes several meals would pass with no overflow of tears. He insisted that this fluctuation in symptoms was a new event and that for several months before investigation tears had overflowed from both eyes at every meal. On the last two occasions he was seen, the total tear output approached the mean normal value and the patient volunteered that his symptoms were progressively improving. This variability in lacrimal secretion makes any assessment of the effects of attempted therapy difficult and it is possible that the patient's condition began a spontaneous remission shortly after observations commenced.

Table *Output of tears (mg.) with a standard taste stimulus applied for 5 minutes*

Subject	*Date*	*Week No.*	*Eye* *Right*	*Left*	*Total*	*Treatment*
Patient	6. 2.69	0	17·6	31·4	49·0	Nil
	14. 2.69	1	17·9	29·7	47·6	Guanethidine right eye (7 days)
	21. 2.69	2	16·6	17·6	34·2	Homatropine left eye (3 days)
	28. 2.69	3	21·1	12·8	33·9	Nil
	14. 3.69	5	18·2	19·6	37·8	Nil
	11. 4.69	9	15·5	10·9	26·4	Nil
	18. 7.69	23	22·3	22·0	44·3	Nil
	25. 7.69	24	25·2	18·0	43·2	Propantheline orally (6 days)
	29. 8.69	29	23·8	17·4	41·2	Propantheline orally (1 day)
	5. 9.69	30	5·0	8·8	13·8	Homatropine right eye (2 hrs)
	19. 9.69	32	12·9	12·9	25·8	Nil
	3.10.69	34	14·2	15·7	29·9	Homatropine right eye (2 hrs)
Six normal young men (mean)			13·7	11·8	25·5	Nil

*For details of treatment, doses, and duration see text.

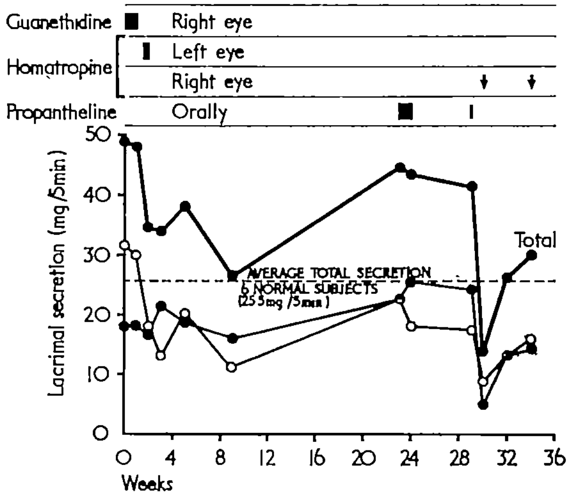

FIGURE *Lacrimal output (right eye, left eye, and total) over a period of* 34 *weeks, without treatment and during treatment with various drugs*

●—● *right eye;* ○—○ *left eye*

Effects of adrenergic blockade

To achieve adrenergic blockade, one drop of a 5 per cent. solution of guanethidine (Ismelin eye drops, CIBA) was instilled into the right eye twice daily for a week. This produced a miosis but no conjunctival injection. During treatment, the patient noticed less lacrimation from the treated eye. However, measurements after a week of treatment (14.2.69, see Table) show no effect on lacrimal secretion.

Anticholinergic agents by mouth

Initial treatment was with propantheline bromide 30 mg. four times daily by mouth, for 6 days before the test on 25.7.69. This medication produced a dry mouth but no constipation or visual blurring. The total tear output was unaffected. On a second occasion, 45 mg. propantheline was taken 6-hourly for 24 hours before testing. (Doses of this order are not commonly tolerated on a long-term basis.) No decrease in lacrimal secretion was demonstrable (see Table, 29.8.69).

Local cholinergic blockade

The close proximity of the lacrimal gland to the superior conjunctival fornix leads to a reasonable expectation that drugs instilled into the conjunctival sac will penetrate to the lacrimal gland and its secretomotor nerve supply. Eyedrops of 1 per cent. homatropine hydrobromide were used. On the first occasion, one drop was instilled into one eye twice daily for 3 days, and on two subsequent occasions measurements were made 2 hours after the instillation of a single dose of 5 drops into one eye. On all three occasions mydriasis and visual blurring were produced. From the Table it appears likely that on 21.2.69 and 5.9.69 a reduction in lacrimal secretion was produced, while on 3.10.69 no such effect is apparent. Since dosimetry is bound to be highly inaccurate when eyedrops are instilled and then diluted and drained away at a variable and unpredictable rate, the failure of effect on the last occasion needs no special explanation. Presumed spontaneous variations in lacrimal output, for example decreased secretion from the left eye on 28.2.69 and 5.9.69, make assessment of drug effects particularly difficult. It was concluded that, although cholinergic blockade probably did reduce lacrimal secretion, this held no therapeutic promise, since the degree of visual difficulty produced by this treatment was unacceptable.

Discussion

The clinical features of this patient are very unusual, in that bilateral paroxysmal lacrimation followed unilateral Bell's palsy. It seems that this phenomenon can be explained only in terms of some central mechanism, as in congenital cases with bilateral symptoms. Possibly a pontine lesion has involved both superior salivatory nuclei together with the nucleus of the right seventh cranial nerve.

Although the syndrome of crocodile tears may cause discomfort and embarrassment, the remedy suggested by Savin (1939), excision of the palpebral portion of the lacrimal gland, is considered too drastic by many surgeons and is reported to have been refused by several patients. Other surgical procedures, such as cutting the chorda tympani, diathermy of the lacrimal ductules, or denervating the lacrimal gland by local dissection, may also be considered unjustified when symptoms are not greatly incapacitating. Blockade of the sphenopalatine ganglion (Savin, 1939; Gottesfeld and Leavitt, 1942) is a lesser procedure and may give substantial relief. Cocaine is applied to the lateral wall of the nose just posterior to the middle concha. If this is followed by several hours' relief of paroxysmal lacrimation, the sphenopalatine ganglion is injected with alcohol. The symptoms may recur after several months, and re-injection may be necessary. On the other hand, Walsh (1957) does not offer active treatment to his patients with paroxysmal lacrimation.

The present observations suggest that attempted pharmacological blockade of lacrimal secretion is not therapeutically useful, since even large doses of anticholinergic agents by mouth produce no measurable effect, while local instillation of homatropine produces impairment of accommodation which is more troublesome than the excessive lacrimation. The bilateral nature of this patient's symptoms makes surgical treatment even less desirable than usual, while drug treatment producing bilateral impairment of accommodation is of course unacceptable.

Summary

A case of bilateral paroxysmal lacrimation following a unilateral Bell's palsy is described. Serial measurements of lacrimal secretion showed spontaneous variations in the severity of the condition. Drug-induced reduction in lacrimal secretion was effective only at the price of unacceptable impairment of accommodation.

My thanks are due to Dr. G. M. Stern for permission to study his patient and to Prof. D. R. Laurence and Dr. D. B. Calne for their criticism of this paper. The work was done during the tenure of a Nuffield Foundation Fellowship.

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Human hair sutures in ophthalmic surgery

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Human hair having been suggested as a possible suture material (Leigh, 1966), we have examined the practicability of its use in ophthalmic surgery since it is so freely available and easily sterilized.

Material

Hairs varying from 6 to 12 in. in length were obtained mostly from women and in some cases from Sikh male members of the department. The hairs selected, after brittle, coarse, or extremely thin hairs had been discarded, were cleaned with 2 per cent. cetavlon, washed in water, wrapped around rubber tubing about 3 in. long to minimize curling, put into a wide-mouthed bottle, and autoclaved for 20 minutes.

Methods of use

(1) *Cataract Surgery*

A total of 100 cases was operated upon, the number of sutures applied varying from one to five (Table I). During the operation the suture ends were kept in place on the face towel by moist cotton swabs. Surgical knots were tied after the operation, and the free ends were cut very short with spring scissors.

Table I *Cataract surgery*

Type of suture (post-placed)	*No. of sutures*					*Total*
	One	*Two*	*Three*	*Four*	*Five*	
Corneo-scleral	42	20	14	4	3	83
Corneo-corneal	—	4	2	3	–	9
Sclero-scleral	—	3	3	2	–	8
Total	42	27	19	9	3	100

During the postoperative period conjunctival congestion was no more than would be expected. Wound closure was adequate in 98 cases, but in two a small knuckle of iris was found to prolapse between the stitches. The anterior chamber formed within 2 days in 97 cases; in three it remained shallow for a longer period and this was found to be associated with choroidal detachment. Wound leakage as the cause of a shallow chamber was excluded by the fluorescein test. Irritation in the eye was complained of in three cases; in these the suture ends were found to be in contact with the overlying palpebral conjunctiva. Relief was obtained by cutting the free ends shorter. Irritation was minimal when the ends were cut very short or buried under the conjunctiva. In no case

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did the knots slip. The sutures were removed on the 12th to 14th day in eighty cases, and removal was easy because of the dark colour and smooth surface. In the other twenty cases the sutures were left buried for 18 months for long-term follow-up, and no untoward reaction or granuloma formation was noted.

(2) *Conjunctival wound repair*

Human hair was used for continuous or interrupted sutures in fifty cases after trephine, iridencleisis, squint, and enucleation operations (Table II).

Table II *Other types of surgery*

Type of suture	*Operation*				*Total*
	Trephine	*Iridencleisis*	*Squint*	*Enucleation*	
Continuous	5	21	11	5	42
Interrupted	–	3	5	–	8
Total	5	24	16	5	50

Foreign body sensation was minimal, and the eyes became quiet in a few days. The sutures were removed on the 5th to 7th day after surgery, and no injection or granuloma formation was noted. The closure of the conjunctival wounds was perfect.

Discussion

Among the various suture materials which have been recommended from time to time are silk (Halsted, 1913), absorbable surgical gut (Hughes, Guy, and Romaine, 1944; Davis, 1944), virgin silk (Hoppenbrouwers, 1962), wire (Hofmann, 1962), and rat-tail tendon (Pischel, 1930; Larmi, 1961; Gopal, Gupta, and Gupta, 1968). Adhesive synthetic material has been used experimentally by Bloomfield, Barnert, and Kanter (1963).

Our good results with human hair were similar to those of Leigh (1966).

The advantages of using human hair are as follows:

(1) It is freely available and easily sterilized by autoclaving.

(2) It is very fine, the average diameter being 87·54 μ or approximately 000,000, so that it passes easily through the eye of the finest needle, and also passes smoothly through the tissues; it is therefore useful for post-placed sutures especially if vitreous leakage is threatened.

(3) It is strong enough to hold the tissues together, is flexible, and does not crack or fray.

(4) It is easily visible for handling and picking up during operations, but the knot produced is small and does not slip.

(5) The capillarity is negligible, so that there is little chance of introducing external infection, and as it is non-irritant it produces hardly any tissue reaction or scarring.

Summary

A method is described of preparing and sterilizing human hair for use as suture material in ocular surgery. The results of a trial in one hundred cases of cataract surgery and fifty cases of extraocular surgery are reported.

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Trachomatous entropion-trichiasis

Case in a 16-month-old infant

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Entropion-trichiasis is seen mainly in adults. It was observed only in old people in South West Africa (Eiselen and Gear, 1960), and in Casamance was rarely present in children under 15 years and not at all in infants (Vellieux, Le Breton, Oliveau, and Larmane, 1959). It was not found amongst 556 trachomatous schoolchildren in Senegal (Vola, 1958). In a Gambian village of 400 inhabitants there were four cases, all in adults (Sowa, Sowa, Collier, and Blyth, 1965). I have seen it infrequently in Gambian children but not hitherto in an infant.

This paper describes severe bilateral entropion-trichiasis in a 16-month-old baby.

Case report

A 16-month-old baby boy was brought to the ophthalmic out-patients clinic with a history of discharging eyes for a year after birth and in-turning eyelashes for the last 5 months. There were two older siblings who had no eye trouble.

Examination

The baby was healthy and well-nourished. His exact age is known because it was recorded by a government midwife; he was still mainly breast fed and the dentition and physical development were consistent with that of a Gambian child of 16 months.

There was severe entropion-trichiasis of both upper eyelids (Fig. 1). Slit-lamp examination of the upper tarsal conjunctivae showed some oedema and hyperaemia with a few papillae and mature follicles in the canthi, and linear scarring in both eyes, worse in the left. In the corneae there was fine trachomatous punctate keratitis with a vascularized opacity in the lower half of each, corresponding to the rubbing lashes. There was no abnormality of the upper limbus. Scrapings from the upper tarsus were examined by the iodine method (Sowa and others, 1965), but no inclusion bodies were found.

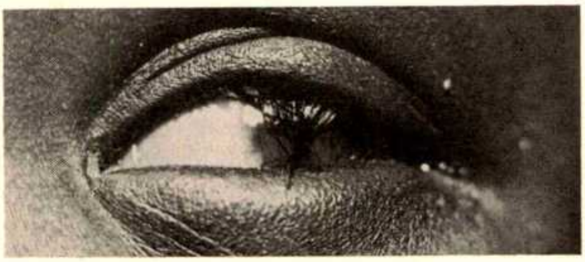

FIGURE *Close-up view of left eye*

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Address for reprints: c/o Dr. L. H. Collier, M.R.C. Trachoma Unit, Lister Institute of Preventive Medicine, Chelsea Bridge Road, London, S.W.1

Treatment

The child was admitted to hospital and was given tetracycline 1 g. daily by mouth for 5 days, and 1 per cent. aureomycin eye ointment twice daily to both eyes. The entropion was then corrected surgically by the method of Trabut (Nataf, 1952).

Summary

A case is reported of bilateral trachomatous entropion-trichiasis in a 16-month-old infant.

I wish to thank Mr. J. Sowa for the photograph.

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Measurement and diagnosis of cyclodeviation by the after-image method

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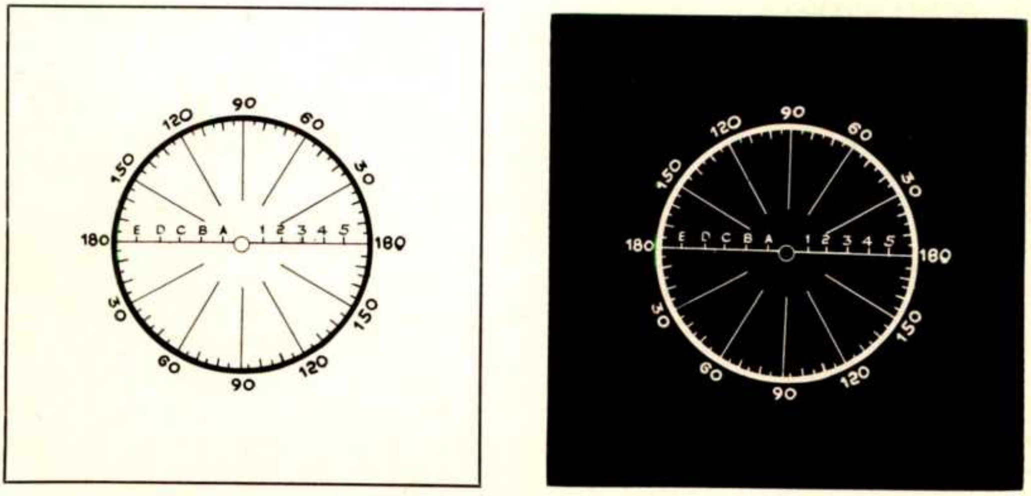
Lesions involving the vertical muscles or their nerve supply usually result in some degree of torsional deviation of the eye which may produce intractable and distressing asthenopia. Although cyclophoria has long been recognized and has been demonstrated with such apparatus as the Maddox rod, Maddox wing, Maddox double prism, and synoptophore, it is nevertheless frequently overlooked. Moreover these tests permit no definite conclusions to be drawn regarding the muscle at fault. A new method of diagnosing cyclodeviation of the eye with the help of the "after-image" test is described below. If it is carried out in three positions of gaze, namely looking straight forwards, looking up, and looking down, the muscle involved can be identified.

Apparatus and method

Two special slides have been devised for use in the synoptophore.

SLIDE A consists of a black circle on a white background, the horizontal diameter of which subtends an angle of 12°. The horizontal diameter is subdivided into divisions of 1° each and in the centre is a tiny circle. On the right side of this central circle the divisions are marked from left to right with the figures 1 to 5, and on the left they are marked from right to left with the letters A to E. The circumference of the circle is marked in degrees, and lines are drawn from 30°, 60°, etc., on the circumference towards the centre like the spokes of a wheel (Fig. 1). These enable the patient to determine the position of the after-image more precisely.

SLIDE B is identical with Slide A except that the circle and other markings are shown in white against a black background (Fig. 2).



FIGS 1 and 2 *White* (A) *and black* (B) *shown side-by-side*

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In most cases either slide can be used, but Slide A is more suitable for patients who experience a more persistent negative after-image, and Slide B for those who experience a more persistent positive after-image. These slides can also be used for the quantitative measurement of anomalous retinal correspondence (Sood, Sen, Jain, and Singh, 1969) and of the angle Kappa.

After the determination of the refractive error and investigation of the type of squint and binocular function, the patient is placed in front of the synoptophore and told to look straight ahead. A vertical after-image is created in one eye, preferably in that with the more defective vision, and the patient is instructed to look at the central spot on the white light. One of the slides described above is now placed before the other eye, and the patient is asked to look at the centre of the circle and to describe the position of the after-image in relation to the markings on the circumference.

The process is repeated after an interval when the previous after-image has completely disappeared, the limbs of the synoptophore being moved first 25° upwards and then 25° downwards.

Conclusion

With the eyes in the primary position, if the vertical after-image points to 90°—90° there is no cyclodeviation. If the upper end of the vertical after-image deviates nasally, excyclodeviation is present; if it deviates temporally, incyclodeviation is present. The degree of deviation can be read off directly from the markings on the circle.

In looking upwards, elevation is produced by the action of the superior rectus and inferior oblique muscles, the intorsion produced by the superior rectus being neutralized by the extorsion produced by the inferior oblique. Intorsion revealed in this position by the after-image suggests weakness of the inferior oblique, and extorsion suggests weakness of the superior rectus.

In looking downwards, depression is produced by the action of the inferior rectus and the superior oblique muscles. Intorsion revealed in this position indicates weakness of the inferior rectus, and extorsion suggests weakness of the superior oblique.

Discussion

Among the various methods used to detect cyclodeviation the Maddox rod and the Maddox wing tests, although simple, are less accurate and cannot measure easily the degree of cyclodeviation in different directions of gaze. With the Maddox double prism, a slight malpositioning of the prism in the spectacle frame or maladjustment of the frame on the face may introduce a considerable error. Our new method is simpler and more accurate and is particularly useful in following cases of vertical muscle palsy due to trauma or some neurological disorder.

Summary

(1) A method of measuring cyclodeviation of the eyes by the after-image test using two special synoptophore slides is described.

(2) By this method it is possible to identify the vertical muscle at fault.

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Electro-mechanical corneal aesthesiometer

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The threshold value of corneal sensitivity to touch is of interest to ophthalmologists and neurologists. The method generally employed for its measurement is credited to von Frey, who produced the test force on the cornea by pushing a long hair against the corneal surface, the force being varied by using a series of hairs of different lengths to determine the threshold for the sensation of touch. The Cochet-Bonnet aesthesiometer (Cochet and Bonnet, 1960) is a modern adaptation of this simple device, in which a single nylon hair in a special holder operated by a thumb mechanism is used to produce all the test forces. Other force-producing systems include a spring as in Schirmer's aesthesiometer (Schirmer, 1963), but the Cochet-Bonnet still seems to be the most popular.

The Cochet-Bonnet instrument, however, has the following drawbacks:

(1) The patient is usually afraid when he sees a hand holding a black rod advancing toward his eye. The natural tendency to blink or flinch can be overcome only by practice or by testing in the dark with infra-red illumination (Bonnet and Millodot, 1966).

(2) The examiner cannot tell when the tip has touched the cornea except by observing the change in the bend of the hair. This reduces the accuracy of the measurement, particularly as the hair is very fine and thus difficult to see.

(3) The nylon hair bends considerably under its own weight and usually takes the form of an arc, particularly when long. For the tip to be at right angles to the corneal surface, the handle must be held pointing slightly upward to compensate for this bend. Other factors, such as previous use and humidity, influence the shape of the hair.

(4) The force applied to the cornea is measured indirectly. The operator must notice when the hair bends and this is the indication that a force has been applied. The manufacturer quotes a force for each length of hair, based on a 5° change of the tip angle due to bending. Fig. 1 shows how the force varies with a change in tip angle for lengths of 18, 38, and 58 mm. Since the operator has no means of measuring the tip angle, a precise estimate of the force applied cannot be made.

(5) The shape of the nylon tip is not reproducible, and this means that the pressure distribution due to the tip's contact with the cornea will not be known.

(6) The nylon hair cannot easily be sterilized.

After studying the Cochet-Bonnet aesthesiometer to find the relationship between the angle of bend and the force produced at the tip (Millodot and Larson, 1967), it was decided to use modern techniques to develop an improved aesthesiometer (Larson, 1968).

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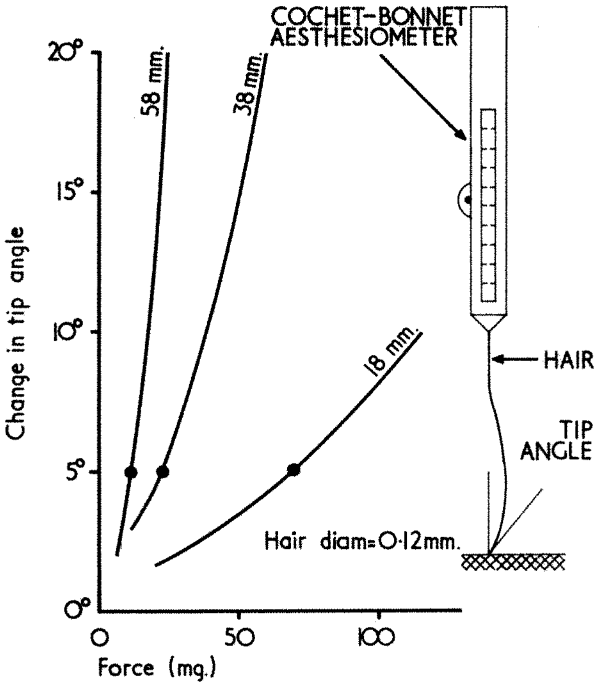

FIG. 1 *Cochet-Bonnet aesthesiometer. Force produced at the tip for given change in tip angle*

The Larson-Millodot instrument (L-M), is characterized by three features:

(1) The probe tip is made of fine platinum wire bent double so that the tip has known and reproducible dimensions. This wire may be flame-sterilized as is the practice in microbiology.

(2) The probe is automatically advanced toward the eye at a constant rate upon the operator's command. When the cornea is touched with a force equal to the test force, the probe is retracted quickly and automatically.

(3) The force applied to the cornea can be set at any value within the range of this instrument and this force will not be exceeded. The range of settings for practical purposes is from 1 to 200 mg., and any force within these limits can be set with an accuracy of ± 0·5 mg.

Operation

The L-M aesthesiometer, Fig. 2*a*, functions in the following way. The platinum probe is mounted on an arm fastened to a torsion wire. A turns-counting dial and gearing are used to twist the wire about its longitudinal axis. The amount of twist in the wire produces the test force. Each division of the dial is equal to 0·5 mg. of force on the most recent instrument. The torsion of the wire holds the arm against a stop and one must exert the rated force to move the arm back from the stop. The backward movement of the arm is detected by a photocell system and this triggers the retracting mechanism that withdraws the carriage. The mechanism described above is mounted on a movable carriage, Fig. 2*b*. A push-button control starts a motor which draws the carriage forward at a fixed velocity. The photocell trigger mechanism releases the motor's clutch when the probe touches the cornea. The carriage is retracted to its starting position by a spring. The moving parts are made as light as possible to minimize inertia. The electronic control system is all solid-state. The net result is a compact unit measuring 22·5 × 12·7 × 10·2 cm. and weighing 5½ lb. (Fig. 2*a*, *b*, overleaf).

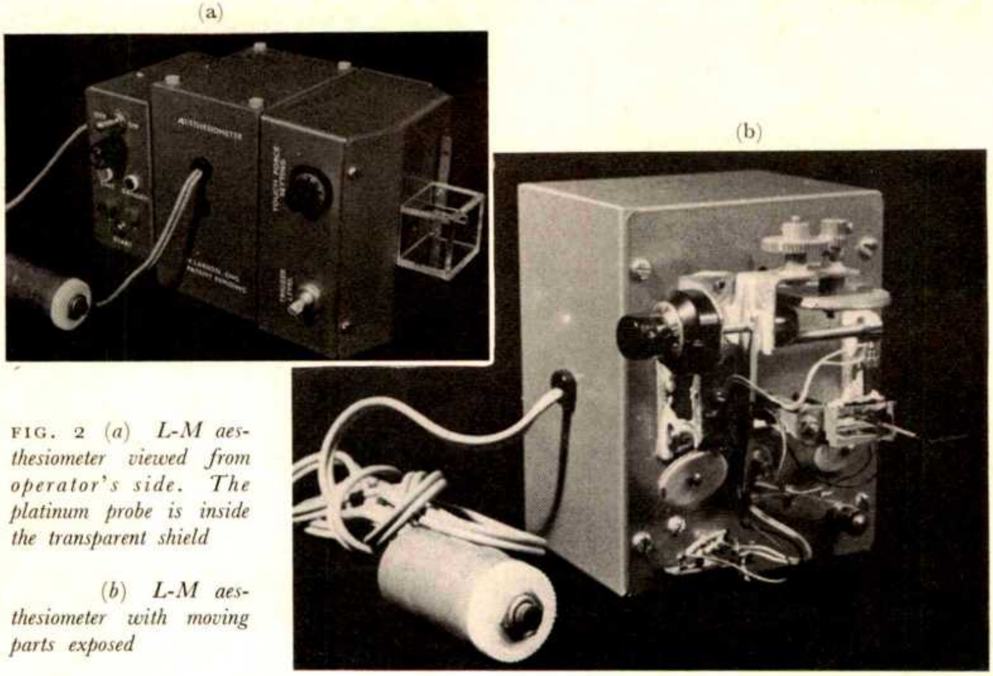

FIG. 2 (*a*) *L-M aesthesiometer viewed from operator's side. The platinum probe is inside the transparent shield*

(*b*) *L-M aesthesiometer with moving parts exposed*

Experimental use

Preliminary work has demonstrated the advantages of this instrument over previous aesthesiometers (Millodot and Larson, 1969). The platinum wire probe is made from very fine wire. This and its proximity to the patient's eye make it so out of focus as to be invisible. When the probe is retracted, it is housed in a clear plastic box; thus the patient can look through the box and fix on some more distant object. The patient is usually less disturbed by this arrangement than by that of the Cochet-Bonnet.

The results of an experiment relating the axial movement of the C-B aesthesiometer to the force developed at the tip are shown in Figs 3*a* and 3*b* (opposite) for the 0·12 mm. and 0·08 mm. diameter hairs respectively. The L-M instrument was first calibrated with weights. Then a small piece of paper was stuck to the tip of the L-M probe, shown on the left of Fig. 4*a*, to give a contact surface for the tip of the C-B hair shown on the right. The C-B was then mounted on a watchmaker's lathe carriage so that, when the leadscrew of the carriage was turned, it moved in the direction of the axis of the handle. The two aesthesiometers were lined up facing each other (Fig. 4*b*). Because of the sag in the hair, the handle of the C-B had to be inclined upwards to make the tips parallel. The voltmeter was used to monitor the movement of the L-M probe (Fig. 4*a*, *b*, opposite).

The C-B was screwed forward until, with the aid of a magnifying glass, the tips were seen to touch. Further rotation of the leadscrew moved the handle of the C-B forward. The dial of the voltmeter indicated when the L-M probe had moved off its stop. A dial on the leadscrew enabled the advance to be estimated to within 0·01 mm. The movement of the L-M probe itself was subtracted from the forward motion of the carriage. The result was the forward motion of the C-B to produce the force set on the L-M. The results of this experiment (Fig. 3*a* and 3*b*) are of value to those using the C-B aesthesiometer.

A very small forward movement is required to produce the rated force. One sees that a movement of only 0·1 mm. will produce the same force as a change in tip angle of 5°,

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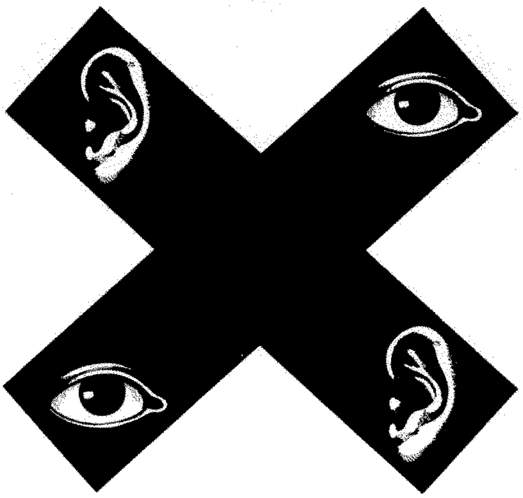

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Fluorescein Sodium BP 1% w/v.
Hydrocortisone/Neomycin Eye and Ear Ointment
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Neomycin BP 0·5% w/w.
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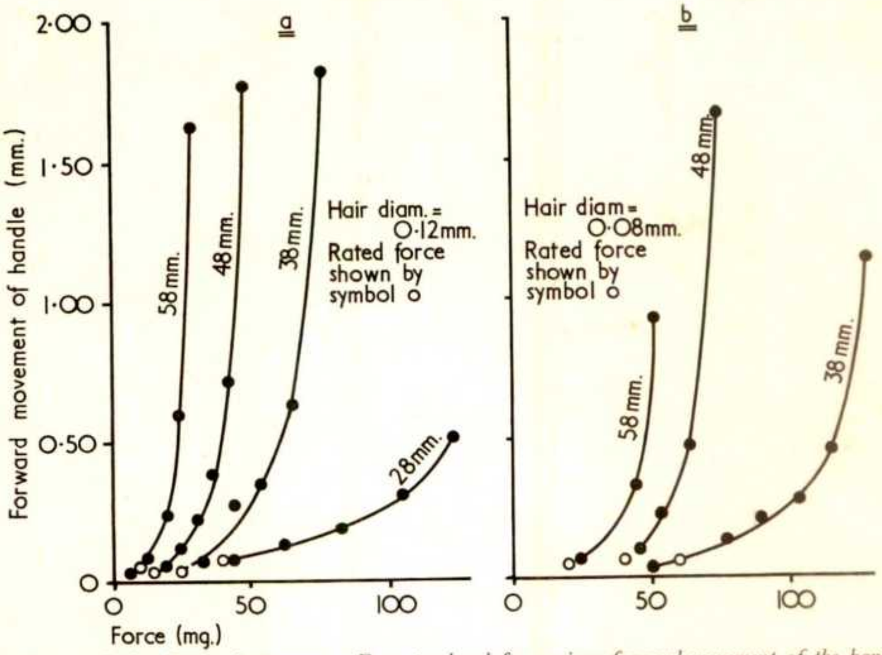
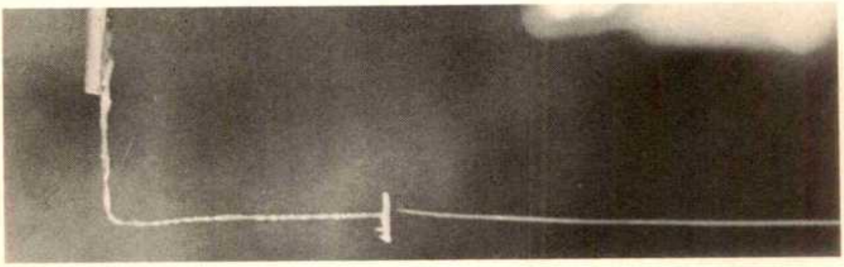
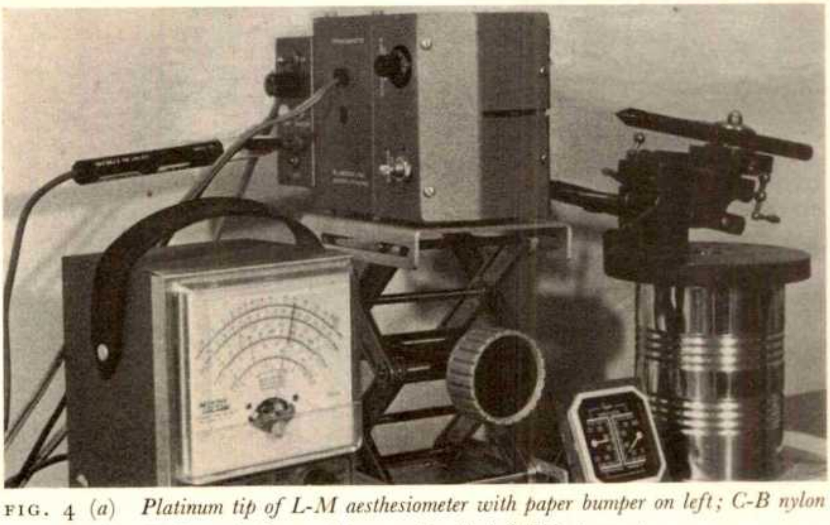


FIG. 3 *Cochet-Bonnet instrument. Force produced for a given forward movement of the handle after the tip has touched* (*a*) Hair diameter 0·12 mm. (*b*) Hair diameter 0·08 mm.



(a)



(b)

FIG. 4 (*a*) *Platinum tip of L-M aesthesiometer with paper bumper on left; C-B nylon tip on right.*
(*b*) *L-M aesthesiometer being used to check C-B instrument*

according to Fig. 1. This apparent inconsistency is due to different test conditions in each case. Fig. 5 illustrates the test conditions (*i*) for Fig. 1, and (*ii*) for Fig. 3, and it can be seen that the direction of application of the force is different. Calculations based on the deflections of beams, as calculated in the strength of materials, indicate that, in fact, the results shown in Fig. 3 are reasonable.

Anyone wanting the lowest possible force for a given bend at the tip should hold the C-B as shown in Fig. 5*c*. Holding it as shown in 5*b* will result in a higher force, perhaps as much as six times higher.

A second experiment with the set-up of Fig. 4*b* was performed to discover if the L-M mechanism produced shock forces at the tip of the probe. It seems reasonable to suppose that the L-M would produce forces at the tip due to the inertia of the probe and the arm supporting it. If these forces were large enough, they would cause the lower force settings of the instrument to be invalid. The C-B was used as a means of showing these impact forces. High speed photographs, 64 frames per second, were taken with a Beaulieu 16 mm. movie camera. The film frames taken before, during, and after the contact of the tips were then examined by projection, one frame at a time, to see if the C-B tip was deflected. No movement of this tip could be seen. From this it can be inferred that the impact forces are lower than the force-measuring ability of the C-B aesthesiometer. During this experiment, the C-B was fixed and the L-M was advanced and retracted automatically in its normal way. The C-B was held as shown in Fig. 5*c*.

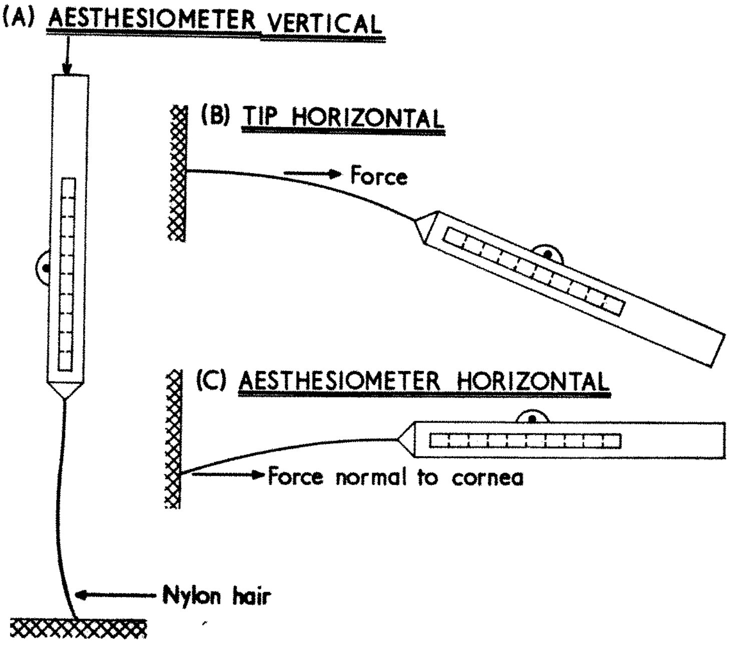


FIG. 5 *Position of Cochet-Bonnet aesthesiometer during experiments*
(*a*) for results in Fig. 1
(*b*) for results in Fig. 3
(*c*) for impact tests

Summary

The corneal aesthesiometer is a device for measuring the threshold of corneal sensitivity. An improved electro-mechanical aesthesiometer, the Larson-Millodot (L-M), is described, and compared with the Cochet-Bonnet (C-B) instrument. Using the L-M as a force-measuring standard, the forward movement of the C-B required to produce a given force

was found for two diameters of hair. An experiment to check the impact forces produced by the L-M is also described. The angle at which the C-B instrument is applied to the cornea was found to have an important influence on the force applied.

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Brit. J. Ophthal. (1970) **54**, 348

Diagnostic Index for Diseases of the Eye

Based on the International Statistical Classification of Diseases (ICD)

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The necessity for an adequate diagnostic index in an eye department, both for in-patients and for those attending the out-patient department, is universally recognized, and a number of different systems are in use throughout the United Kingdom. In the busy atmosphere of an out-patient clinic it is essential that the diagnostic number or code be readily available to the medical personnel so that they can enter the diagnosis and the code number on the patients' case notes at the time of examination. Alternatively, if the doctor does not do the coding, it must be easy for the secretary or clerk to find the number quickly and efficiently so that it can be entered when the letter or report about the patient is typed before the case notes are returned to file.

In designing any diagnostic index nowadays, it is necessary to plan one which will be suitable for data processing and computer analysis in the future, and also one which may be generally accepted throughout the country for national surveys and other research projects.

In some places the classification of diseases from *Ophthalmic Literature* is in use, but this is only suitable for small eye departments (Blach, 1967). Another system based on the "Standard Nomenclature of Diseases and Operations" (1961) published for the American Medical Association has been used in a number of departments, including until recently Edinburgh. The Moorfields Eye Hospital "Code for Diagnoses and Operations", which has both topographical and aetiological sections, as well as a code of operations, is suitable for large eye hospitals and is now in use in a number of centres. In addition, many eye departments and hospitals have their own private systems.

In Great Britain the classification of diseases adopted for general use in all hospitals and accepted by the Ministry of Health in England and Wales and the Scottish Home and Health Department in Scotland, is based on the International Classification of Diseases (ICD)" approved by the World Health Organization. The Eighth Revision (1967) of the ICD is now incorporated into two volumes entitled "Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death"; volume one contains mainly the tabular list of inclusions, and volume two an alphabetical index of diseases and nature of injuries. This classification, which is basically a three-digit system with some

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four-digit subcategories, is used throughout the country for in-patient hospital returns and has been given trials for out-patient use.

The ICD code contains a small and rather inadequate section for diseases of the eye in the division on the nervous system and sense organs. Only twenty numbers, 360–379, have been allotted to eye conditions, but all medical disorders which may have eye manifestations or complications have in addition their own diagnostic number in other parts of the code outside the Eye section; for example Sarcoidosis is 135 and Diabetes Mellitus is 250, but Diabetic Retinopathy is not mentioned under diseases of the eye. The ICD classification having been found inadequate in its present form for use in large eye departments, the International Council of Ophthalmology has recommended yet another system entitled "Coding System for Disorders of the Eye" (suggested abbreviation CDE). This index, based on an original system devised by Dr. S. Franken of Utrecht and now modified by Drs. Schappert-Kimmijser and Colenbrander, was finally published in 1968 in English after approval by the International Council of Ophthalmology and the International Federation of Ophthalmological Societies who recommend its use for ophthalmological purposes in member countries (Kimmijser, Colenbrander, and Franken, 1968). The CDE is a six-digit system containing between five and six thousand separate items. It is laid out in alphabetical order over 163 pages covering every possible eye condition and syndrome. Although this would be suitable for use in big departments having abundant secretarial assistance, it is not a practical proposition for everyday use in a busy eye department in Great Britain.

In Edinburgh, therefore, we have now examined again the ICD code with its two sections "Inflammatory Diseases of the Eye" (360–369) and "Other Diseases and Conditions of the Eye" (370–379) under the general heading (VI) "Diseases of the Nervous System and Sense Organs". In order to fit into it all the eye conditions we encounter we have altered the aetiological headings to topographical headings (*i.e.* 360 Conjunctivitis becomes Conjunctiva) and have used the fourth digit in each of the twenty categories available, so giving a possible two hundred different diagnostic items. In order to include all the parts of the eye and adnexa, it was necessary to change the designation of three of the official numbers as follows:-

362 from 'hordeolum' to 'orbit'

371 from 'corneal opacity' to 'miscellaneous visual disturbance'

378 from 'other diseases of the eye' to 'visual pathway'.

This modified ICD system has been in use in Edinburgh for the past year and has also been tried out in a number of other centres in Great Britain. A final revision has now been made in the light of comments from users, and omissions from the original draft which have been discovered have now been included in the final code. Because of the interest shown in this system by a number of eye units throughout the country, it was decided to seek publication in the *British Journal of Ophthalmology* so that those interested would find it readily available to them. It would also be advantageous if the authorities could be persuaded to accept the suggested alteration to the Eye Section because, at the present time, the 1967 edition of the Manual incorporating the ICD system is in use for in-patient returns to the Ministry of Health and the Scottish Home and Health Department, so that this modified system can, at the moment, be used only for local diagnostic coding in the eye departments themselves and not on official returns.

Before tabulating the diagnostic index in full, the following ideas incorporated in the modified code are worth pointing out:

(1) The ·0 and ·1 subcategories of each of the twenty numbers are given to the commonest conditions under each heading, *e.g.* cataract is 374·0, concomitant divergent squint is 373·1.

(2) Some conditions have been cross-referenced under different topographical sections *e.g* phakolytic glaucoma (374·4) is included under both the lens section and the glaucoma section. This is to allow for quick and easy finding of the condition by different diagnosticians.

(3) Certain common eponyms or syndromes are listed because medical staff may use different terms to describe the same condition, and all such terms should be available to a lay person who may be doing the coding.

(4) Eye conditions which have their own number outside the 360–379 range, *i.e.* viral diseases of the conjunctiva; neoplasms; trauma, etc., have been included in the tabulated lists under the appropriate part of the eye, and a list of the commonest medical conditions with ocular manifestations is given separately in Appendix I.

(5) With regard to trauma, the extra digit (·0 to ·9) is given to the same part of the eye throughout, as listed in Appendix II. This extra digit is shown in parenthesis after each heading of the main list. For neoplasms, however, as also seen in Appendix II, the assignment of the extra digits is a little different in order to include neoplastic lesions of the extraocular structures.

(6) In all categories an indefinite heading is included under ·9.

I am greatly indebted to our departmental secretaries Mrs. Anne Roger and Mrs. Susan Hauge for their assistance in compiling the diagnostic index and in the preparation of this paper.

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Classification

360	CONJUNCTIVA (.0)
360.0	Acute, non-viral conjunctivitis
360.1	Allergic conjunctivitis (including spring catarrh)
360.2	Chronic conjunctivitis
360.3	Late effects of conjunctivitis (concretions; granuloma, etc.)
360.4	Degenerations of conjunctiva (pingueculae, etc.)
360.5	Phlyctenular conjunctivitis and keratoconjunctivitis
360.6	Spontaneous subconjunctival haemorrhage
360.7	Symblepharon
360.8	Conjunctival cysts
360.9	Other and unspecified diseases of conjunctiva
053.0	Herpes zoster conjunctivitis
054.0	Herpes simplex conjunctivitis
076	Trachoma
077	Late effects of trachoma
078.1	Epidemic keratoconjunctivitis
078.2	Adenoviral keratoconjunctivitis
078.9	Viral conjunctivitis (unspecified)
098.2	Gonococcal conjunctivitis and ophthalmia neonatorum
190.0	Malignant neoplasm of conjunctiva
224.0	Benign neoplasm of conjunctiva
N870.0	Open wound of conjunctiva
N921.0	Contusion wound of conjunctiva (haemorrhage, etc.)
N930.0	Conjunctival foreign body
N940.0	Burn of conjunctiva
N960	Adverse effect of chemical agents (specify)

361	LIDS (.1)
361.0	Blepharitis (squamous; ulcerative)
361.1	Allergic conditions (oedema, etc.)
361.2	Abscess of lid
361.3	Ectropion
361.4	Entropion
361.5	Stye, hordeolum
361.6	Chalazion; Meibomian, tarsal cyst, etc.
361.7	Ptosis
361.8	Trichiasis
361.9	Other and unspecified diseases of the lid
053.1	Herpes zoster ophthalmicus involving lids
054.1	Herpes simplex of lids
079.0	Molluscum contagiosum
172.1	Malignant melanoma, lids, and canthi
173.1	Other malignant neoplasms of lids
216.3	Benign neoplasm of skin of lid (papilloma, angioma etc.)
272.0	Xanthoma (xanthelasma and all diseases of lipid metabolism)
706.2	Sebaceous cyst of lid
744.8	Congenital anomalies of lids (excluding epicanthus – 373.4)
757.1	Benign naevus of skin of lid
N870.1	Open wound of lids
N921.1	Contusion wound of lids (black eye)
N930.1	Subtarsal foreign body
N940.1	Burn of lids
N960	Adverse effect of chemical agents (specify)

362	ORBIT
362.0	Orbital cellulitis
362.1	Endocrine exophthalmos (thyrotoxic, non-infiltrative)
362.2	Endocrine exophthalmos (thyrotrophic, infiltrative)
362.3	Exophthalmos, proptosis (not caused by tumour)
362.4	Reticuloses involving orbit
362.5	Pseudotumour of orbit
362.6	Mucocele invading orbit
362.7	Foreign body retained in orbit
362.8	Orbital decompression
362.9	Other and unspecified diseases of orbit
190.8	Malignant neoplasm of orbit
224.8	Benign neoplasm of orbit
N802.4	Fracture (blowout, etc.) of orbit

363	CORNEA (.2)
363.0	Infective, non-viral corneal ulcer and hypopyon
363.1	Corneal scarring from ulcers etc.
363.2	Exposure keratitis; neuroparalytic keratitis
363.3	Degenerative conditions (band keratitis; descemetocele)
363.4	Marginal and catarrhal keratitis
363.5	Corneal graft
363.6	Superficial punctate keratitis
363.7	Disciform keratitis
363.8	Corneal dystrophy (keratoconus, etc.)
363.9	Other and unspecified conditions of cornea
053.2	Herpes zoster keratitis
054.2	Herpes simplex keratitis (dendritic, etc.)
090.3	Interstitial keratitis
190.2	Malignant neoplasm of cornea
224.2	Benign neoplasm of cornea
260.1	Xerophthalmia and keratomalacia
695.3	Rosacea keratitis
734.9	Kerato-conjunctivitis sicca (Sjogren's)
744.6	Congenital conditions of cornea (megalocornea; dermoids, etc.)
N870.2	Open wound of cornea
N921.2	Contusion wound of cornea (abrasion, etc.)
N930.2	Corneal foreign body
N940.2	Burn of cornea

364 IRIS AND CILIARY BODY (.3)

364.0 Iritis and iridocyclitis
364.1 Heterochromic cyclitis
364.2 Lens-induced uveitis
364.3 End result of anterior uveitis (synechiae, etc.)
364.4 Sympathetic uveitis
364.5 Pupillary abnormalities (Adie; Horner's; Argyll Robertson pupil, etc.)
364.6 Mydriasis (including traumatic)
364.7 Miosis (including congenital)
364.8 Cysts of iris and ciliary body
364.9 Other and unspecified conditions of iris and ciliary body

190.3 Malignant neoplasm of iris and ciliary body

224.3 Benign neoplasm of iris and ciliary body

744.4 Coloboma of iris and ciliary body
744.5 Aniridia

N870.3 Open wound of iris and ciliary body
N921.3 Contusion wound of iris and ciliary body (hyphaema)
N930.3 Foreign body in iris or ciliary body

365 CHOROID (.4)

365.0 Choroiditis (active)
365.1 Choroiditis (healed)
365.2 Disseminated choroiditis
365.3 Degenerations (sclerosis, etc.)
365.4 Drusen, colloid bodies
365.5 Detachment of choroid
365.6 Choroidal haemorrhage
365.7 Choroideremia
365.8 Choroidal naevus
365.9 Other and unspecified conditions of choroid

190.4 Malignant neoplasm (primary and secondary) of choroid

224.4 Benign neoplasm of choroid

744.4 Coloboma of choroid

N870.4 Penetrating wound involving choroid
N921.4 Contusion wound of choroid (tears, etc.)
N930.4 Foreign body in choroid

366 VITREOUS (.5)

366.0 Vitreous floaters
366.1 Vitreous detachment
366.2 Vitreous haemorrhage
366.3 Retinitis proliferans (fibrous tissue in the vitreous)
366.4 Recurrent vitreous haemorrhage (Eales's disease)
366.5 Asteroid bodies and synchisis scintillans
366.6 Vitreous infection (endophthalmitis)
366.7 Persistent hyperplastic primary vitreous
366.8 Retrolental fibroplasia
366.9 Other and unspecified conditions of vitreous

N870.5 Open wound involving vitreous (loss, etc.)
N921.5 Contusion injury including haemorrhage
N930.5 Foreign body retained in vitreous

367 OPTIC NERVE (.6)

367.0 Optic neuritis and retrobulbar neuritis
367.1 Neuromyelitis optica
367.2 Optic atrophy
367.3 Ischaemic optic neuropathy
367.4 Papilloedema (plerocephalic)
367.5 Pseudopapilloedema
367.6 Papilloedema (not plerocephalic)
367.7 Toxic amblyopias; optic neuropathy (tobacco amblyopia, etc.)
367.8 Physiological cupping of disc (*see* 375)
367.9 Other and unspecified conditions of optic nerve

190.6 Malignant neoplasm of optic nerve

224.6 Benign neoplasm of optic nerve

744.7 Congenital anomalies of optic nerve (opaque nerve fibres, etc.)

N870.6 Penetrating injuries involving optic nerve
N930.6 Foreign body in optic nerve
N950.0 Injury of optic nerve

368 LACRIMAL SYSTEM

368.0 Infantile dacryocystitis, congenital obstruction, etc.
368.1 Acute dacryocystitis
368.2 Chronic dacryocystitis and nasolacrimal obstruction
368.3 Other obstructions, ampullary, etc.
368.4 Epiphora—no obvious cause
368.5 Dacryoadenitis, infective
368.6 Dacryoadenitis, associated with other disease (mumps, etc.)
368.7 Diminished secretion (excluding Sjogren's, 734.9)
368.9 Other and unspecified conditions

190.7 Malignant neoplasm of lacrimal gland

224.7 Benign neoplasm of lacrimal gland

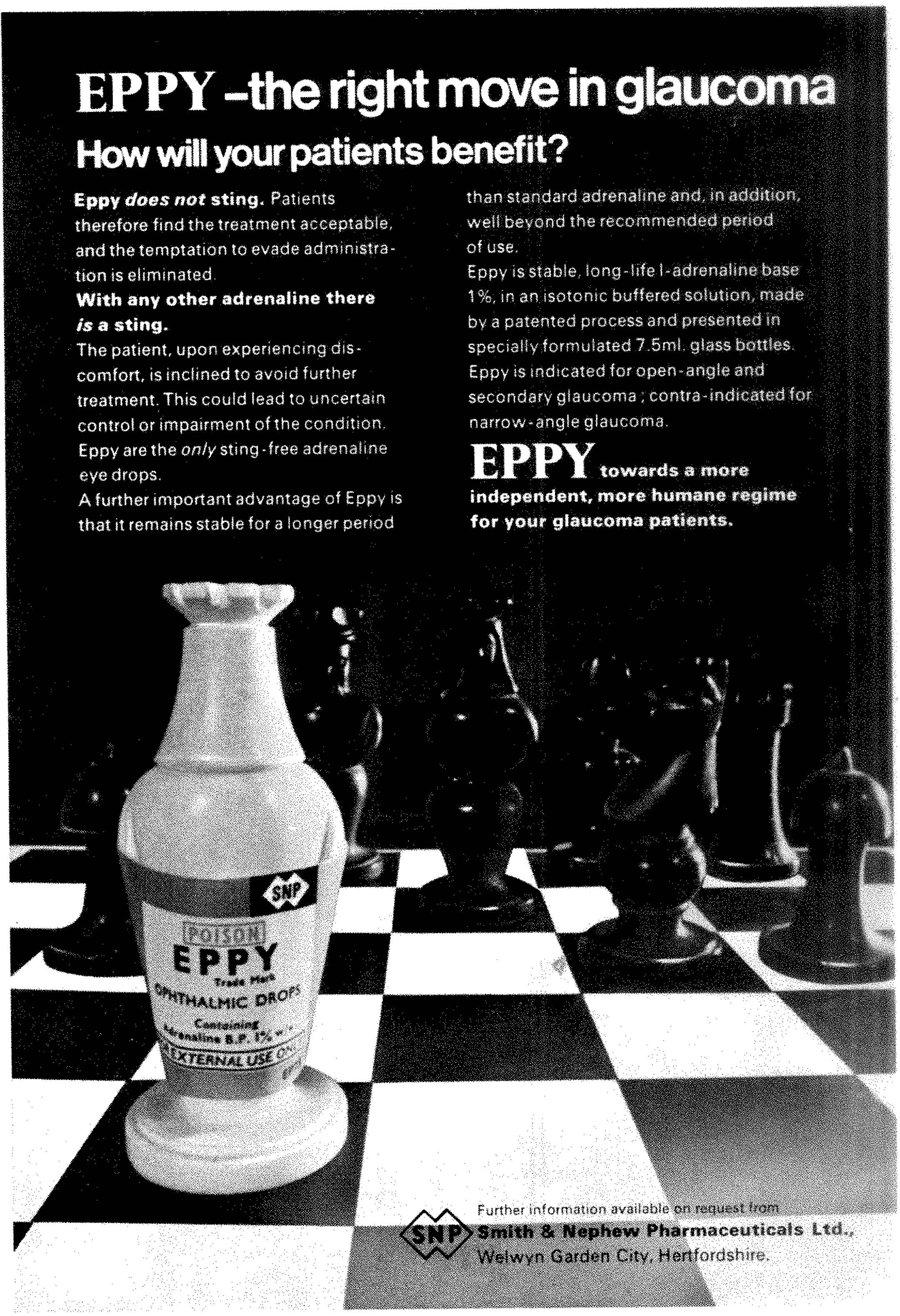
369 SCLERA (.7)

369.0 Episcleritis
369.1 Scleritis
369.2 Sclerokeratitis
369.3 Sclero-malacia perforans
369.4 Staphyloma (ciliary, etc.)
369.9 Other and unspecified conditions of sclera

N870.7 Penetrating injury of sclera
N921.7 Contusion of sclera
N930.7 Foreign body in sclera
N940.7 Burn of sclera

370 REFRACTIVE CONDITIONS

370.0 Emmetropia
370.1 Hypermetropia
370.2 Myopia
370.3 High myopia (over −6 D sph.)
370.4 Astigmatism
370.5 Anisometropia



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BIOCHEMISTRY OF THE EYE

Edited by Clive Graymore

Institute of Ophthalmology
University of London, England

May 1970, xiv + 784 pp., 60., 240s.
SBN 12.297146.9

Until the second world war the eye was virtually ignored as an object of biochemical interest. During the last twenty-five years, however, studies of the eye and of the chemical basis of vision have provided valuable information relating to other tissues and to biochemistry in general.

The papers in this volume provide a comprehensive and critical analysis of these recent studies of this complex organ, describing a variety of biochemical circumstances.

The book is intended primarily for ocular biologists and clinical ophthalmologists; it will also be of value to all researchers interested in the chemical basis of living matter.

Contents

D. M. Maurice and M. V. Riley: The cornea. D. F. Cole: Aqueous and ciliary body. John F. R. Kuck, Jr.: Chemical constituents of the lens. John F. R. Kuck, Jr.: Metabolism of the lens. John F. R. Kuck, Jr.: Cataract formation. E. R. Berman and Mary Voaden: The vitreous body. Clive N. Graymore and David Yi-Yung Hsia: Inborn errors of metabolism affecting the eye. D. S. McLaren: Nutritional aspects of the eye. C. D. B. Bridges: Biochemistry of vision. Clive Graymore: Biochemistry of the retina. Author index. Subject index.

BIOCHEMISTRY OF THE RETINA

Edited by Clive Graymore, Institute of Ophthalmology, University of London, England

1965, xiv + 172 pp., 60s.
SBN 12.297150.7

This book is based on the 1st International Symposium on the Biochemistry of the Retina held in London. It fills the need for a comprehensive basic book on this rapidly expanding subject.

Retinal biochemistry, which is now considered a specialty in its own right, embraces the molecular architecture of the eye, the nature and distribution of the enzyme sequences the eyes contain, and the functions of the individual layers in the eye.

Biochemistry of the Retina includes information from related areas as well as a review of the major topics within the subject, making it of interest to researchers in allied fields as well as retinal biochemistry.

ACADEMIC PRESS
London and New York

Berkeley Square House, Berkeley Square, London WIX 6BA, England
111 Fifth Avenue, New York, N.Y. 10003, USA

370 *Refractive conditions* (*continued*)

370.6	Irregular astigmatism due to conical cornea, scarring, etc.
370.7	Presbyopia
370.8	Accommodation disorders
370.9	Other and unspecified conditions

371 MISCELLANEOUS VISUAL DISTURBANCES

371.0	Amblyopia ex anopsia
371.1	Amaurosis fugax
371.2	Visual symptoms associated with migraine
371.3	Angiospasm (retinal, etc.)
371.4	Ocular and retro-ocular pain (unknown origin)
371.5	Monocular diplopia
371.6	Functional and hysterical syndromes
371.7	Malingering and "compensationitis"
371.8	Colour vision defects
371.9	Other and unspecified conditions
260.0	Night blindness
781.0	Hemianopia and other field defects
781.2	Photophobia
791	Headaches

372 PTERYGIUM

372.0	Pterygium
372.1	Pseudopterygium

373 OCULAR MOTILITY

373.0	Concomitant convergent squint
373.1	Concomitant divergent squint
373.2	Convergence insufficiency
373.3	Pseudosquints (including epicanthus) and observation for squint
373.4	Duane's and other retraction syndromes
373.5	Paralytic squint
373.6	A and V syndromes
373.7	Vertical squint
373.8	Phorias
373.9	Other and unspecified conditions (including diplopia of indeterminate cause and supranuclear lesions)
300.8	Miner's nystagmus
330.9	Muscular dystrophies and myopathies
733.0	Myasthenia gravis
781.1	Nystagmus (including latent)

374 LENS (.8)

374.0	Senile cataract, lens opacities
374.1	Pre-senile cataract
374.2	Cataract secondary to other ocular disease
374.3	Metabolic/endocrine cataract
374.4	Hypermature cataract and complications (phakolytic glaucoma, etc.)
374.5	Dislocation of lens (non-traumatic; Marfan's syndrome, etc.)
374.6	Traumatic dislocation of lens
374.7	Aphakia
374.8	Exfoliation of lens capsule
374.9	Other and unspecified conditions of lens
744.3	Congenital cataract (including rubella cataract)
N870.8	Penetrating injury to lens
N921.8	Contusion injury to lens
N930.8	Foreign body in lens (retained in eye)

375 GLAUCOMA

375.0	Acute congestive (angle-closure and narrow-angle glaucoma)
375.1	Simple glaucoma
375.2	Secondary glaucoma (post-inflammatory)
375.3	Post-traumatic glaucoma
375.4	Absolute glaucoma
375.5	Thrombotic glaucoma
375.6	Steroid-induced glaucoma
375.7	Aphakic glaucoma
375.8	Observation for glaucoma
375.9	Other and unspecified glaucomas
376.8	Physiological cupping of optic disc (*see* 367)
374.4	Phakolytic glaucoma (*see* 374)
744.2	Congenital glaucoma (buphthalmos)

376 RETINA (*Detachment, etc.*) (.6)

376.0	Detachment of retina (myopic, etc.)
376.1	Detachment of retina (traumatic)
376.2	Retinal cysts
376.3	Retinoschisis
376.4	Central serous retinopathy
376.5	Coats's disease (exudative retinopathy)
376.6	Macular oedema, holes, cysts, etc.
376.7	Macular dystrophies (heredo-macular degeneration, etc.)
376.8	Retinitis pigmentosa and other abiotrophies
376.9	Other and unspecified non-vascular conditions of retina
190.5	Malignant neoplasm (retinoblastoma)
224.5	Benign neoplasm (hamartomas; phakomatoses, etc.)
365.4	Colloid bodies (*see* 365)
366.8	Retrolental fibroplasia (*see* 366)
744.4	Coloboma
N870.6	Penetrating injury involving retina
N921.6	Contusion injury, commotio, etc.
N930.6	Foreign body retained in retina

377 RETINA (*Vascular disease, etc.*)

377.0	Diabetic retinopathy
377.1	Macular degeneration (senile, haemorrhagic, disciform, etc.)
377.2	Myopic macular degeneration
377.3	Arteriosclerotic retinopathy
377.4	Hypertensive retinopathy
377.5	Retinopathy associated with blood dyscrasias
377.6	Retinal vein thrombosis (central and branch)

377	*Retina etc.* (*continued*)
377.7	Retinal arterial occlusions (central and branch)
377.8	Retinal vasculitis
377.9	Other and unspecified vascular diseases of retina
366.4	Eales's disease (*see* 366)
446.3	Temporal arteritis

378	VISUAL PATHWAY
378.0	Optic nerve compression syndromes (intracranial not orbital)
378.1	Chiasmal compression syndromes from tumours, aneurysms, etc.
378.2	Lesions of optic tracts (non-vascular)
378.3	Lesions of optic radiations (non-vascular)
378.4	Lesions of visual cortex (non-vascular)
378.5	Vascular lesions affecting intracranial optic nerve
378.6	Vascular lesions affecting chiasma, tracts, and geniculate bodies
378.7	Vascular lesions affecting optic radiations and cortex
378.8	Visual field defects associated with head injury
378.9	Other and unspecified conditions
226.2	Craniopharyngioma and other benign neoplasms of pituitary
253.0	Pituitary eosinophil adenoma (acromegaly)
253.2	Pituitary chromophobe adenoma

379	BLINDNESS
379.0	Blindness both eyes, specifically defined (VA: 6/60; field: 20° and less)
379.1	Blindness both eyes, not specifically defined (inability to work)
379.2	Blindness one eye, specifically defined
379.3	Blindness one eye, not specifically defined
379.4	Registered blind
379.5	Registered partially sighted
379.6	Blind child
379.7	Enucleated eye (not trauma)
379.8	Both eyes enucleated (not trauma)
379.9	Other and unspecified causes

744	CONGENITAL ANOMALIES
744.0	Anophthalmos
744.1	Microphthalmos
744.2	Buphthalmos
744.3	Cataract
744.4	Coloboma
744.5	Aniridia
744.6	Congenital conditions of cornea (megalocornea, dermoids, etc.)
744.7	Congenital anomalies of optic nerve (opaque nerve fibres, etc.)
744.8	Congenital anomalies of lids (excluding epicanthus—373.4)
744.9	Other and unspecified conditions
270.8	Albinism

TRAUMA, TOXIC EFFECTS OF DRUGS, ETC.

N800	Fracture of vault of skull
N801	Fracture of base of skull
N802	Fracture of face bones
N850	Concussion
N854	Unspecified head injury
N870	Open wound of eye and orbit (*see* part of eye)
N871	Enucleation following injury
N910	Surface injury to face
N920	Contusion of face, scalp, and neck (except eyes)
N921	Contusion of eye and orbit (*see* part of eye)
N930	Foreign body (*see* part of eye concerned)
N940	Burn of eye (*see* part of eye concerned)
N960–N979	Adverse effects of medicinal agents (specify) *e.g.* chloroquine, N961.3 Promazine, N967.9

NO OCULAR ABNORMALITY

Y02.9	Eye investigations nothing abnormal discovered

Appendix I

MEDICAL CONDITIONS

011	Pulmonary tuberculosis
056	Rubella
090	Congenital syphilis
130	Toxoplasmosis
135	Sarcoidosis
147	Malignant neoplasm nasopharynx
162	Malignant neoplasm lung
174	Malignant neoplasm breast
191	Malignant neoplasm brain
192	Malignant neoplasm central nervous system (other parts)
208	Polycythaemia vera
216	Benign neoplasm of skin
225.0	Benign neoplasm of brain
227	Haemangioma and lymphangioma
242	Thyrotoxicosis
250	Diabetes mellitus
253	Diseases of pituitary gland
255	Diseases of adrenal glands
272	Disorders of lipid metabolism
279	Metabolic disorders (other)
280	Anaemia (iron deficiency)
281.0	Pernicious anaemia
287	Purpuras
289.0	Secondary polycythaemia
309	Mental disorders
330.9	Muscular dystrophies

Medical Conditions (continued)

340	Multiple sclerosis
346	Migraine
350	Facial paralysis
351	Trigeminal neuralgia
390	Rheumatic disease
400	Malignant hypertension
401	Essential benign hypertension
403	Hypertensive renal disease
410	Acute myocardial infarction
430	Subarachnoid haemorrhage
431	Cerebral haemorrhage
432	Carotid disease
433	Cerebral thrombosis
434	Cerebral embolism
435	Basilar-vertebral disease
437	Cerebral aneurysm
440	Arteriosclerosis
446.0	Polyarteritis nodosa
446.3	Temporal arteritis
461	Acute sinusitis
503	Chronic sinusitis
580	Acute nephritis
582	Chronic nephritis
712	Rheumatoid arthritis
733.0	Myasthenia gravis
742	Congenital hydrocephalus

Appendix II

NEOPLASMS

190	MALIGNANT NEOPLASM OF EYE
190.0	Conjunctiva
190.1	Lid
190.2	Cornea
190.3	Iris and ciliary body
190.4	Choroid
190.5	Retina
190.6	Optic nerve
190.7	Lacrimal gland
190.8	Orbit
190.9	Unspecified

224	BENIGN NEOPLASM OF EYE
224.0	Conjunctiva
224.1	Lid
224.2	Cornea
224.3	Iris and ciliary body
224.4	Choroid
224.5	Retina
224.6	Optic nerve
224.7	Lacrimal gland
224.8	Orbit
224.9	Unspecified

TRAUMA

N870	OPEN WOUND OF EYE AND ORBIT
N870.0	Conjunctiva
N870.1	Lid
N870.2	Cornea
N870.3	Iris and ciliary body
N870.4	Choroid
N870.5	Vitreous
N870.6	Retina/optic nerve
N870.7	Sclera
N870.8	Lens
N870.9	Unspecified

N871	ENUCLEATION (traumatic)
N910	SUPERFICIAL INJURY to face, scalp, and neck
N920	CONTUSION INJURY of face, scalp, and neck

N921	CONTUSION INJURY OF EYE AND ORBIT
N921.0	Conjunctiva
N921.1	Lids
N921.2	Cornea
N921.3	Iris and ciliary body
N921.4	Choroid
N921.5	Vitreous
N921.6	Retina
N921.7	Sclera
N921.8	Lens
N921.9	Other and unspecified
N950	Injury of optic nerve

N930	FOREIGN BODY IN EYE AND ADNEXA
N930.0	Conjunctiva
N930.1	Lid
N930.2	Cornea
N930.3	Iris and ciliary body
N930.4	Choroid
N930.5	Vitreous
N930.6	Retina/optic nerve
N930.7	Sclera
N930.8	Lens
N930.9	Unspecified
362.7	Foreign body in orbit

N940	BURNS CONFINED TO EYE
N940.0	Conjunctiva
N940.1	Lid
N940.2	Cornea
N940.7	Sclera
N940.9	Other and unspecified

Brit. J. Ophthal. (1970) 54, 356

Book reviews

Clinical Neuro-ophthalmology. Vols 1 to 3, 3rd ed. By F. B. WALSH and W. F. HOYT. 1969. Pp. 2763, figs, refs. Williams and Wilkins, Baltimore; Livingstone, Edinburgh. (£55).

The arrival of the long-awaited third edition of this famous *Textbook* will be welcomed by all ophthalmologists, neurologists, and neurosurgeons. It is a particular pleasure that the senior author (in his 73rd year) has accomplished this task, and has introduced a dedicated and distinguished colleague who will nurture it for the benefit of future generations of neuro-ophthalmologists.

The third edition retains the general pattern of its predecessors, but has been completely re-written and brought up to date. The size has been increased to 3,000 pages, and the text has been divided into three volumes, a comprehensive index of 72 pages being included at the end of each volume. The subject matter is presented with clarity and depth and all recent work of importance is included. The whole book has been made more readable by the omission of many of the illustrative case histories and the inclusion of the authors' opinions on certain subjects. The illustrations have been painstakingly collected to complement the erudition of the text, and in a few cases the presentation of an important clinical point is enhanced by subtle and humorous undertones.

Volume I is made up of seven chapters which discuss the sensory, motor, and autonomic systems, congenital anomalies, and hereditary disorders, and includes a chapter on the optic nerve head. The chapter on the visual sensory system is a review of modern neurophysiology and stresses certain aspects such as the concepts evoked by the work of Hubel and Wiesel in Boston. Similarly the chapter on the ocular motor system comprises an excellent review of this subject including a section on abnormalities of the eyelids. Clinicians may, however, be disappointed that Gerlier's disease merits two paragraphs whereas vertical nystagmus is ascribed but three lines. An excellent chapter on the pupil merits study by all clinicians who use this compact system for measurement and diagnosis.

The remaining chapters retain the highest academic standard and include discussion on the nature of chromosomal anomalies, inborn errors of metabolism, neurolipidoses, and the pigmentary retinopathies. The chapter on the optic disc is well illustrated and the classification of disc oedema recommended here could well eliminate some of the present confusion.

Included in Volume II are chapters on metabolic and toxic diseases, the disorders of muscle, and extensive chapters on infectious diseases, and vascular and circulatory disorders. The chapter on disorders of muscle gives wide coverage of this increasingly complex subject, with a consideration of the current status of progressive external ophthalmoplegias; it introduces many conditions such as nemaline and central core myopathy with which few ophthalmologists are familiar. The chapter on infectious diseases includes 76 pages on syphilis, but also stresses recent advances of importance such as the aetiological implications of Dawson's subacute sclerosing encephalitis.

The final chapter on vascular lesions is especially recommended owing to the quality of the radiographs, photographs of pathological specimens, diagrams, and fundus photographs.

The final volume discusses tumours, trauma and hypoxia, neurotoxic substances, and the ocular signs of neurasthenia, hysteria, and malingering. The chapter on tumours includes a section on the phakomatoses, and this is followed by descriptions of tumours of the eye, the orbit, and the central nervous system. Systemic conditions with orbital involvement (*e.g.* lymphomata) and their management are fully described, so that further recourse to a textbook on medicine is unnecessary. Cranio-cerebral trauma and hypoxia constitute a chapter which will be of particular value to paediatric ophthalmologists, but should be read by all those who have to deal with head injuries. The final chapter on neurotoxic agents comprises a formidable list, ranging from barbiturates to Barracuda poisoning, and closes with concepts of "multidimensional neuropathology".

This textbook is of the highest calibre; it is as vital for the ophthalmologist with an interest in neurology as for the neurologist with ocular interests, and serves to emphasize the common ground of these two specialties. The elaboration of the science of neurophysiology, biochemistry, and genetics, and the introduction of electron microscopy, pupillography, and electromyography makes this text an excellent launching pad for the next decade. The breadth and depth of the subject matter and the extensive bibliography make this work the definitive reference book on neuro-ophthalmology for all libraries, ophthalmic hospitals, and ophthalmic departments.

The main disadvantage is the exorbitant price (£55) which will put this textbook out of the range of many prospective purchasers. Furthermore, the size and weight (19 lbs) make transportation difficult and will restrict its use either to libraries or to the confines of the study!

However, without reservation, I recommend an investment in this book which will impart to the owner some of the enthusiasm and fascination for this unique specialty, which has inspired the authors throughout their Herculean venture.

Handbook of Ocular Therapeutics and Pharmacology. 3rd ed. By P. P. ELLIS and D. L. SMITH. 1969. Pp. 251, refs. Mosby, St. Louis; Kimpton, London. (97*s*.)

The book is divided into two main sections. The first opens with a description of the factors governing the preparation of drops and ointments with general considerations such as drug penetration and toxicity. It is pointed out that most eyedrops and ointments used in the United States are now commercially prepared and sold already packaged in suitable containers, droppers, etc.

Several chapters deal with the principles of the main types of therapy: steroids, antibiotics, and agents acting on the autonomic nervous system. Following this is a series of chapters dealing with the therapy of the principal ocular diseases from an anatomical and pathological point of view. Thus there are, for example, chapters on diseases of the lids, conjunctiva, and lacrimal apparatus, and on glaucoma, infections, and optic neuritis.

The second section comprises an alphabetically arranged list of all the usual drugs encountered in ophthalmology with pharmacological notes on each.

This is a valuable work of reference which every ophthalmologist would appreciate in the consulting room and it is particularly recommended for hospital residents who need quick access to accurate and well-advised information on their many therapeutic problems. One of the most pleasing things about the book is the wealth of factual material, such as the dosage and mode of administration of drugs.

Symposium on Retina and Retinal Surgery. NEW ORLEANS ACADEMY OF OPHTHALMOLOGY. 1969. Pp. 406, 372 figs, 12 col. pl., refs. Mosby, St. Louis; Kimpton, London. (265*s*.)

One method of keeping abreast of current developments in one's subject is to attend symposia on specialized topics or to read the papers presented at such symposia. The New Orleans Academy of Ophthalmology organized a symposium on the retina and retinal surgery in 1968, emphasis being placed on the practical aspects of this subject. The 22 papers which were presented, and the round-table discussion which followed, cover several aspects of retinal surgery in which recent advances have been made.

Several speakers discussed the examination of the peripheral retina and vitreous, and the various forms of degeneration which may occur in these structures, while the several techniques for producing choroido-retinal adhesion were discussed and compared. The current management of difficult types of retinal detachment (giant retinal breaks, massive preretinal fibroplasia, diabetic detachment) are described and it is encouraging to read that these types, which until recently were considered virtually untreatable, are now amenable to therapy, albeit complicated therapy at times.

As Schepens indicated in his paper on the evolution of concepts related to retinal detachment, we have come a long way since Gonin's original work on the sealing of retinal breaks. Anatomical re-attachment of the retina can now be achieved in a high percentage of cases. It is to be hoped that in future symposia of this type we shall be equally encouraged by the functional results that at present elude us in so many cases.

Any surgeon interested in the treatment of retinal detachments will find much stimulating material in this volume.

Précis d'ophtalmologie. By H. Saraux and B. Biais. 1969. Pp. 978, 528 figs, 3 col. pl., bibl. Masson, Paris. (NE150)

This new textbook of ophthalmology is divided into six parts: methods of examination, diseases of the eye and adnexa, neuro-ophthalmology, the eye and general disease, trauma, and therapy. The subject is covered succinctly and in an up-to-date manner and is suitable for the junior ophthalmologist requiring a textbook in French. The illustrations vary considerably in quality and there are several misprints in the text. In spite of these minor criticisms, which it is hoped will be corrected in future editions, this book is a useful addition to French ophthalmic literature.

Proceedings of the Centennial Symposium, Manhattan Eye, Ear, and Throat Hospital. Vol. 1. Ophthalmology. Edited by A. I. Turtz. 1969. Pp. 331, 247 figs, refs. Mosby, St. Louis; Kimpton, London. (247*s*.)

This symposium was designed in honour of the Centennial Anniversary of the Manhattan Eye, Ear and Throat Hospital, supported by financial grants from two foundations. The book, which is rather expensive, although it is most successful in giving authoritative views on many of the chief growing points in our subject, is divided into six sections: (1) New concepts in ocular therapy, (2) Controversial areas in ocular surgery, (3) Paediatric ophthalmic problems, (4) Ophthalmic plastic surgery, (5) New techniques in ophthalmology, (6) Complications in ocular surgery.

The 32 subsections naturally vary in quality and detail, but they are of special value in keeping the general ophthalmic surgeon abreast of recent developments, and the specialist in touch with fields other than his own.

The symposium was obviously planned with imagination and intelligence, and is a credit not only to the participants but also to the great hospital which it was called to honour.

Parson's Diseases of the Eye. 15th ed. By S. Duke-Elder. 1969. Pp. 597, 453 figs, 21 col. pl. Churchill, London. (75*s*.)

The publication of the 15th edition of this work is in itself a tribute to its continuing and well-deserved popularity. Short of being a text-book, it provides a comprehensive and lucid guide to practically the whole field of ophthalmology. It is most useful perhaps to ophthalmic house-surgeons, especially to those aspiring to ophthalmology as a career, who will find therein a basic guide to the first principles of approach and basic information on a very wide range of ocular malfunction and disease. It is equally valuable as a source of reference to casualty officers, general practitioners, and, indeed, to any who wish a concise and clear exposition of some problem or disease with which they are not familiar.

This new edition, appearing some 5 years after its predecessor, has been extensively amended to keep up to date with current trends and developments, particularly perhaps in the field of the various retinopathies, and equally successfully elsewhere.

The production is well up to the high standard we have come to expect of its publishers, who surely must also be warmly complimented on having been able to keep the price within such reasonable bounds. The paper-back E.L.B.S. (English Language Book Society) edition at 35*s*. (£1.75 decimal), while obviously not so durable for library use, is a quite outstanding bargain.

An Anthology of Ophthalmic Classics. Edited by J. E. LEBENSOHN. 1969. Pp. 407. Williams and Wilkins, Baltimore; Livingstone, Edinburgh. (£7 10*s.*)

These ophthalmic classics, originally published between 1267 and 1952, appeared in their present form, with historical notes and a short biography of each author, in the periodical *Survey of Ophthalmology* between 1956 and 1969. Their collection into one volume makes fascinating reading. This book is thoroughly recommended to both residents and established ophthalmologists.

The Human Visual Evoked Response. Method and Theory. By N. W. PERRY, JR. and D. G. CHILDERS. 1969. Pp. 187, figs, bibl. Thomas, Springfield, Ill. ($14)

The introduction of electronic averaging devices has made possible the detection of very small bioelectric potentials and their separation from potentials from neighbouring structures. In this way it is possible to detect a change of activity in the occipital cortex due to stimulation of the eye. Many workers have studied this phenomenon in recent years and this book is an attempt to review and correlate their efforts. The authors are well fitted to the task as they have considerable experience in both the experimental and clinical aspects of the subject.

The early studies elicited the response with a flash of light but subsequently more sophisticated patterned stimuli were used. These later methods also involved a change in illumination, so that the only information that one could reasonably expect to gain was that a change of illumination had been perceived. This is a considerable achievement when the information can be gained in no other way. The attempts to obtain more information, by varying the stimulus, by picking up the response from different parts of the scalp, or by analysing the signal in various ways, are described in some detail. Unfortunately, the results of different workers are often different or even contradictory. This is to be expected in the early days of a complex technique using sophisticated electronic processing.

The authors claim that the book is clinically orientated, but this is far from true for the main body of the work. There is a brief final section on clinical applications which is uninformative and speculative. A very helpful feature, however, is a very extensive bibliography referenced outside the text. It will be invaluable to the worker in the field and will prove a useful source of reference for anyone interested in a particular aspect.

There is no doubt that this response is already clinically useful. Only a brief note is made of stimuli that involve no change in illumination, but it is likely that this technique offers far more possibilities, so much so that it will replace the crude flashing method. As yet the test is available in a few centres only and even here its clinical use can hardly be said to be established. If anyone wishes to shop around for equipment to set up a unit, there is an appendix with the names and addresses of suitable suppliers, but almost all are in the United States.

Protection of Vision in Children. By A. PATZ and R. E. HOOVER. 1969. Pp. 172, 83 figs. Thomas, Springfield, Ill. ($10)

It is estimated that, of the 40,000,000 schoolchildren in the United States, a quarter have or will have some visual defect. This slim volume may seem in size a feeble attempt to approach this problem, but it is an excellent and rewarding book. It is not written for the ophthalmologist but there can be no ophthalmologist who would not benefit by reading it. It is addressed to everyone who is interested in children and is full of sound practical advice concerning many aspects of paediatric ocular care. The methods of assessing vision in children and the role of various specialties in its protection are discussed, and the management of the child with poor vision is reviewed. Great stress is laid on the prevention of childhood accidents and a clear guide to first aid is given. There is a somewhat redundant glossary, but this in no way detracts from this valuable work.

Ophthalmic Ultrasound. Proceedings of the Fourth International Congress of Ultrasonography in Ophthalmology, Philadelphia, Pennsylvania. Edited by K. A. GITTER, A. H. KEENEY, L. K. SARIN, and D. MEYER. 1969. Pp. 374, 296 figs, bibl. Mosby, St. Louis; Kimpton, London. (265*s*.)

There may be many ophthalmologists who are conversant with the relative merits of TAU and SIMU, who will tolerate the term "overview", and who will accept small change from 13 guineas; they will already have bought this book. The others may like to know that it represents the proceedings of the fourth international congress of ophthalmic ultrasonography. There are papers on basic instrumentation, basic biology, ocular biometrics, ocular diagnosis, and ocular therapy. As in all such symposia, the contributions vary from the excellent to the uninformative.

In addition to the 44 papers, which are presented in a most attractively printed, illustrated, and bound volume, there is an extensive bibliography. For the worker in the field this book will be essential and for anyone interested in the field it will be useful. It cannot be expected that the clinical ophthalmologist will cope with the complexities of the physical sciences called on to aid his human faculties. For him this book tells him more about ophthalmic ultrasonography than he would reasonably wish to know.

Notes

International Society for Clinical Electroretinography

VIII ISCERG Symposium, Pisa, September 7 to 11, 1970

The main topics of this symposium will be "Correlation between histology and electrophysiology of the retina" (introduced by Prof. W. K. Noell, Buffalo, U.S.A.) and "Electrodiagnostic procedures in visual pathology of children" (introduced by Docent Birgitta Zetterstrom, Stockholm, Sweden). Free papers will also be accepted.

Non-members of ISCERG who are interested in the Symposium are invited to write for further information to Prof. Dr. Alberto Wirth, ISCERG Symposium 1970, Clinica Oculistica Universitaria, 56100 Pisa, Italy.

Israel Ophthalmological Society

VIII Symposium, December, 1970

The VIII Symposium, to be held in Tel Aviv on December 16 to 18, will be devoted to paediatric ophthalmology. The main topics will be:

1. Muscular anomalies and amblyopia.
2. Education of visually handicapped children.
3. Neonatal defects.
4. Tumours.

For further information please write to Prof. O. Kurz, The Israel Ophthalmological Society, Beilinson Hospital, Petah Tikva, Israel.

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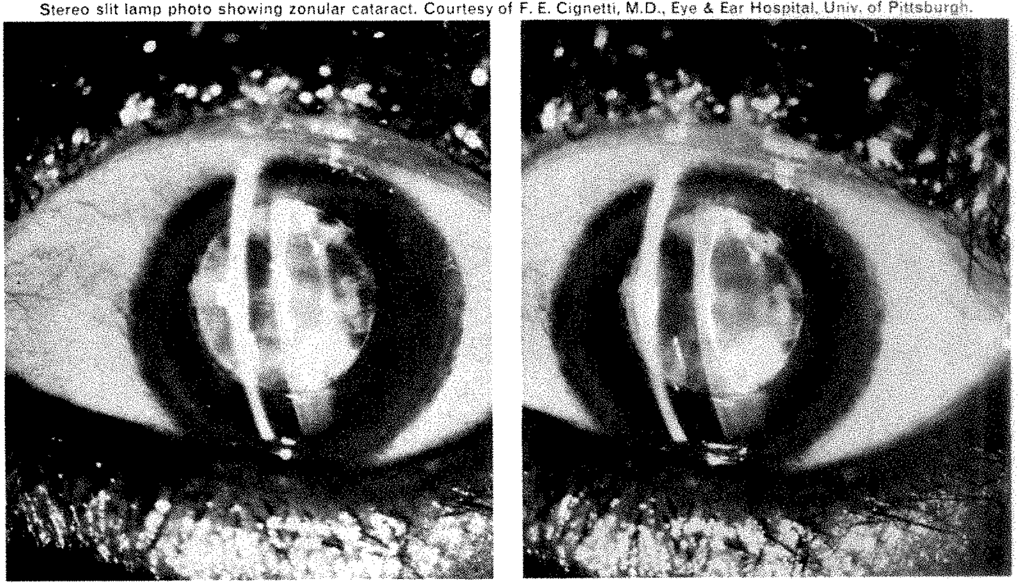

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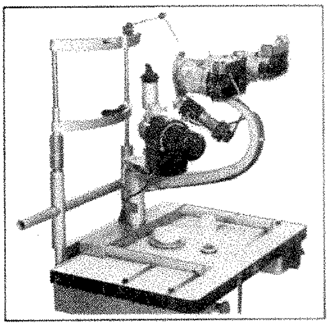

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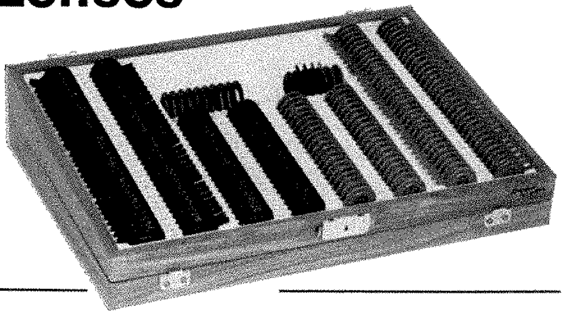

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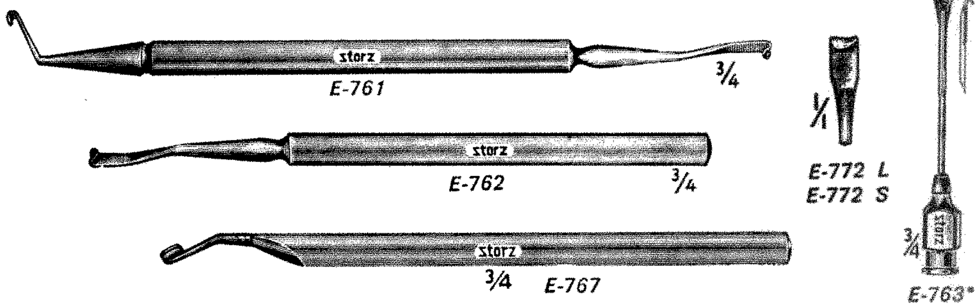

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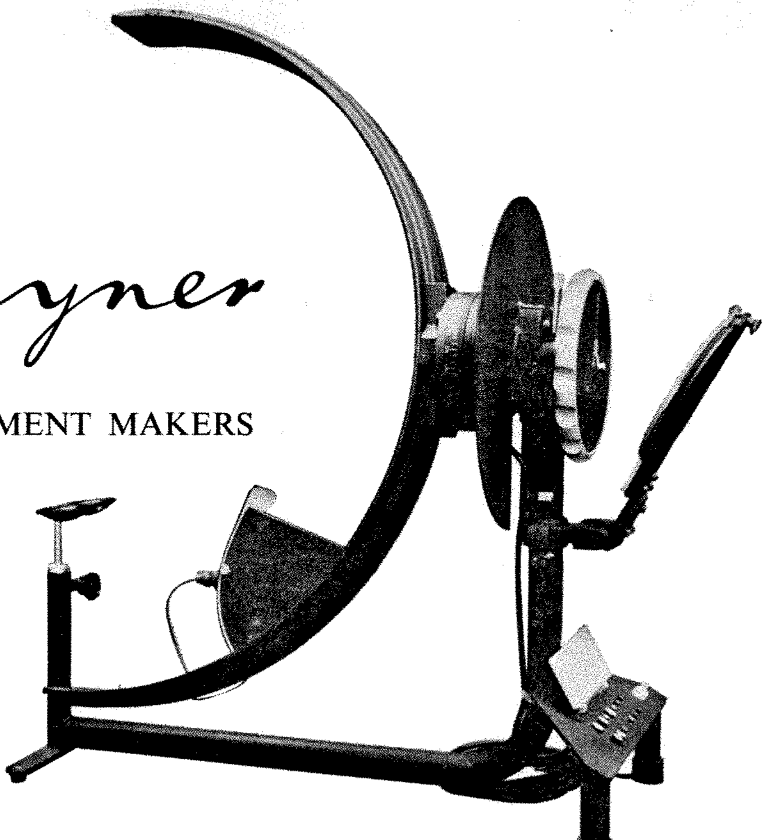

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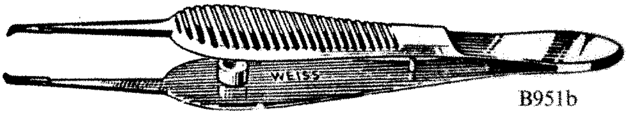

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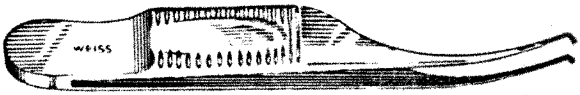

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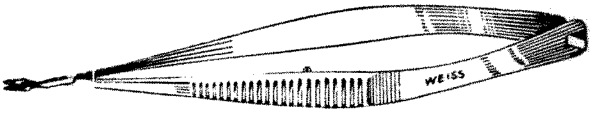

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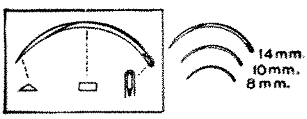
B874. **Forceps,** corneal, Barraquer's *do.*
B1053. **Scissors,** miniature, for removal of corneal sutures, etc.



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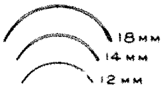

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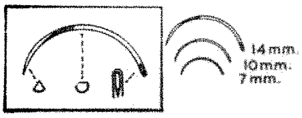

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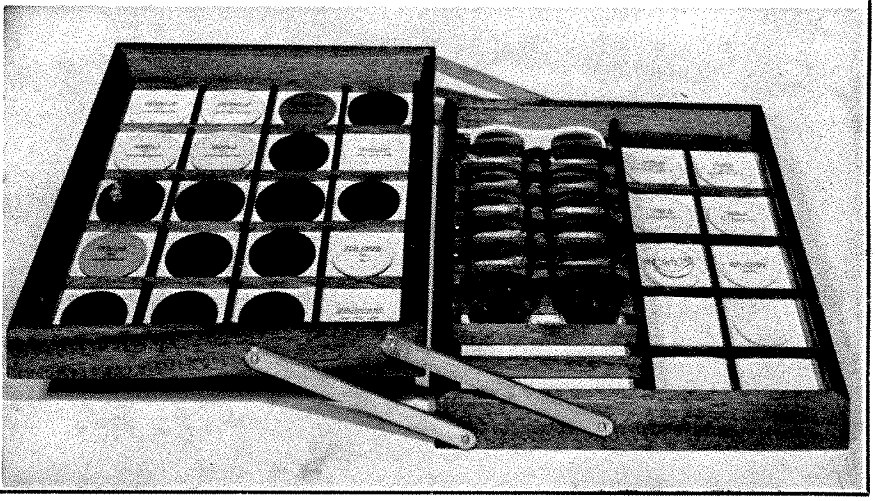

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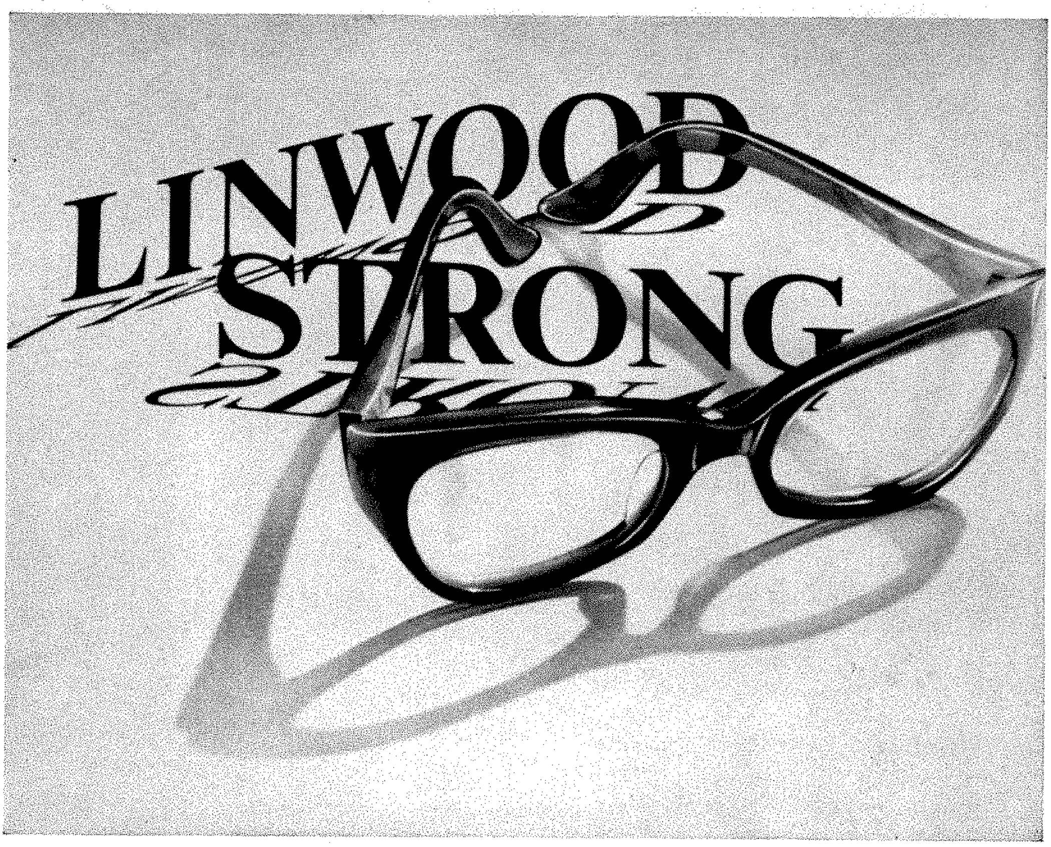

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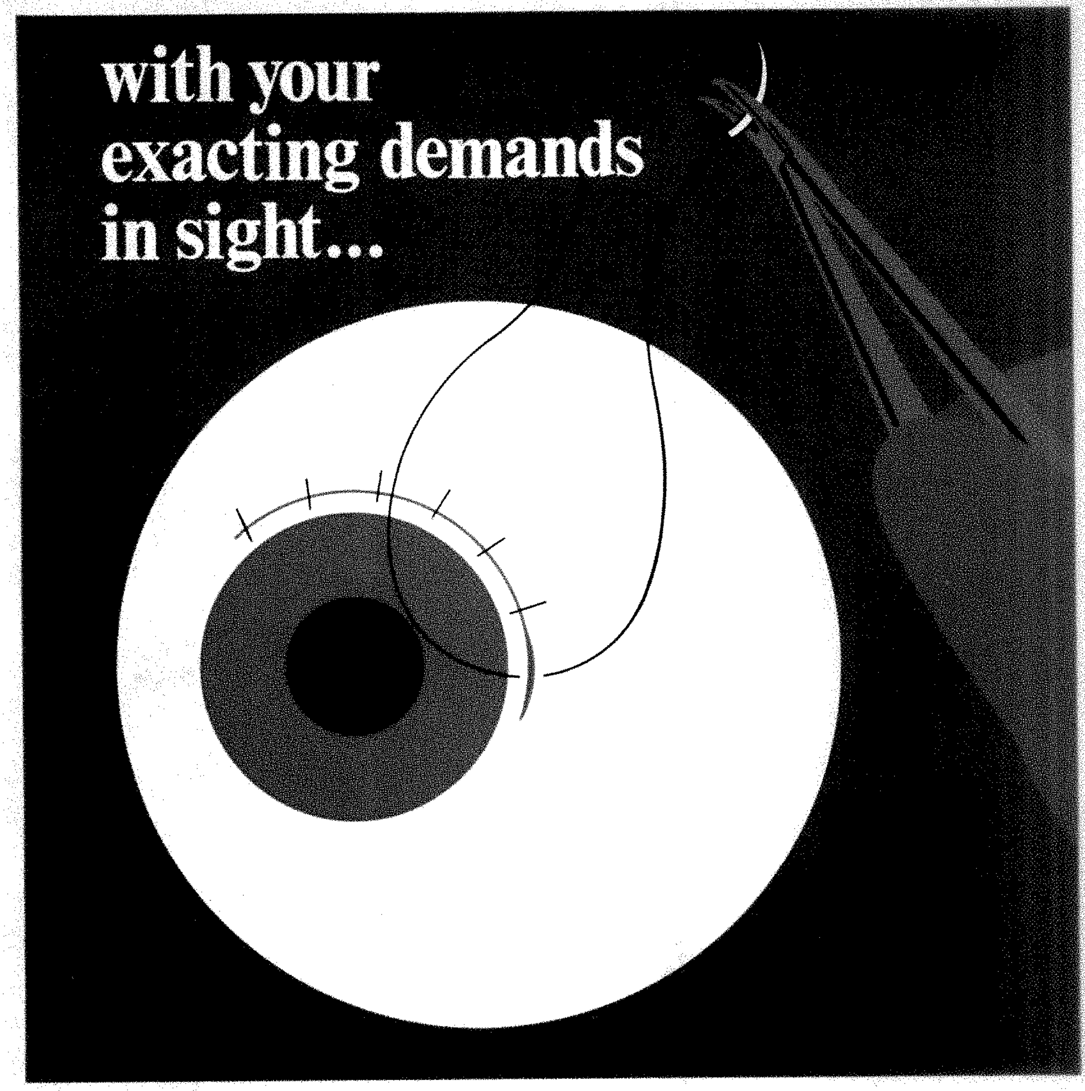

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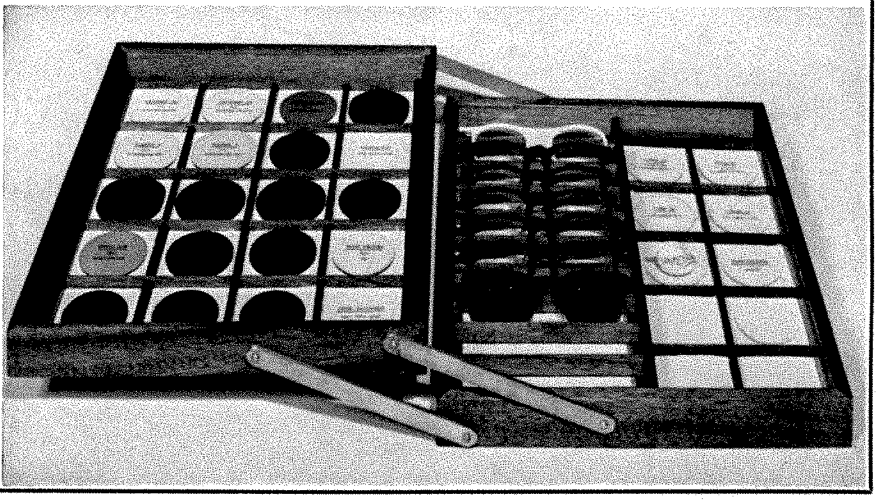

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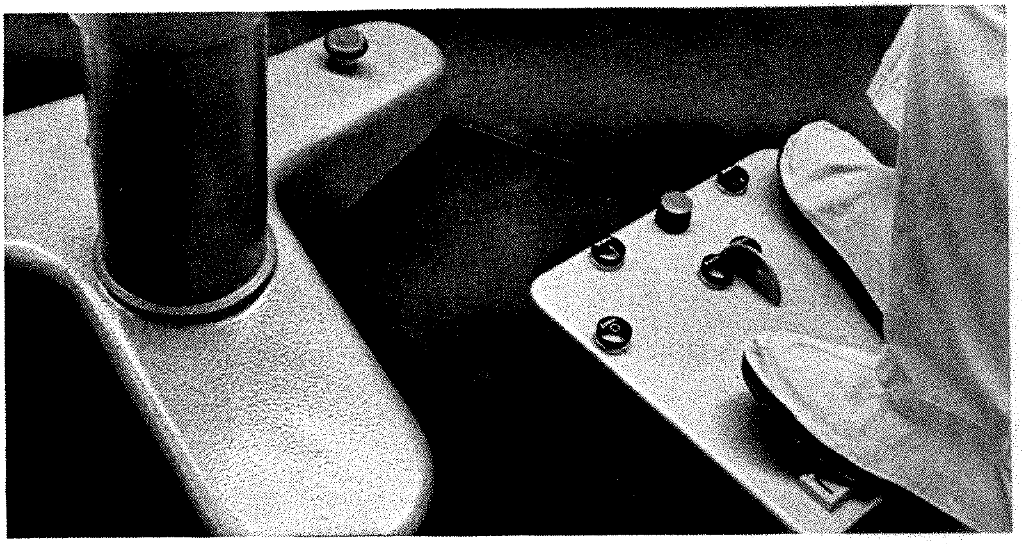

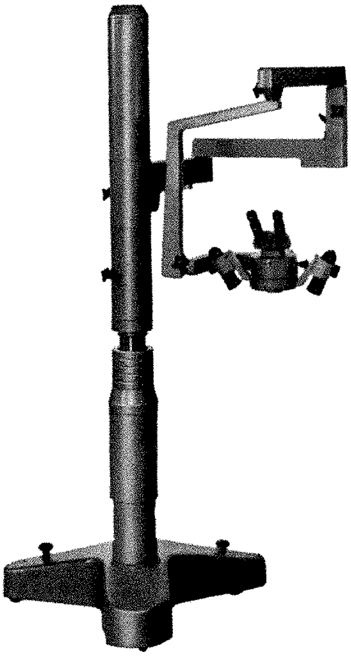

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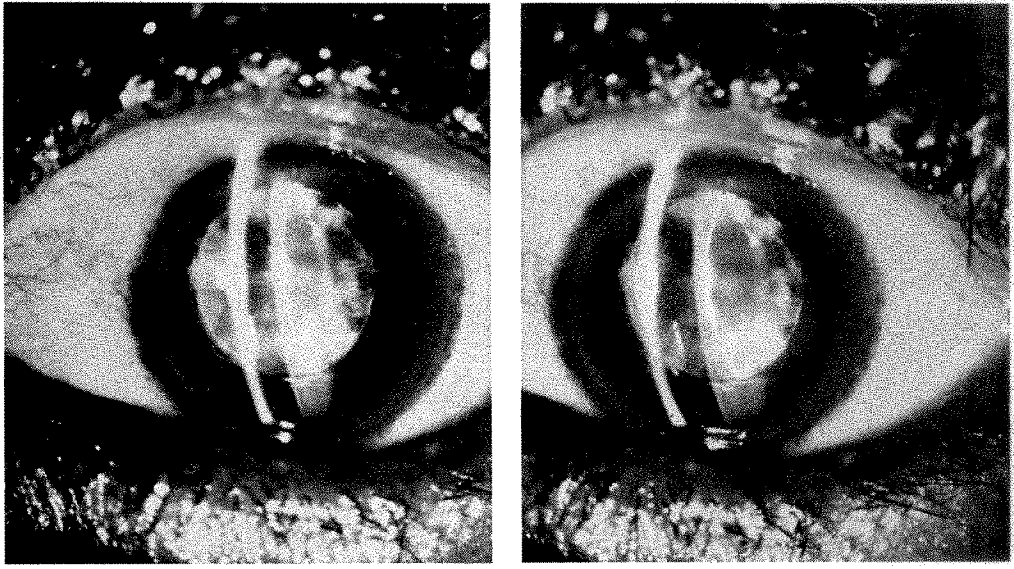

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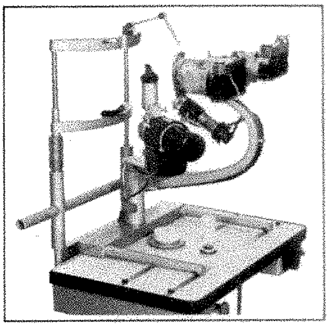

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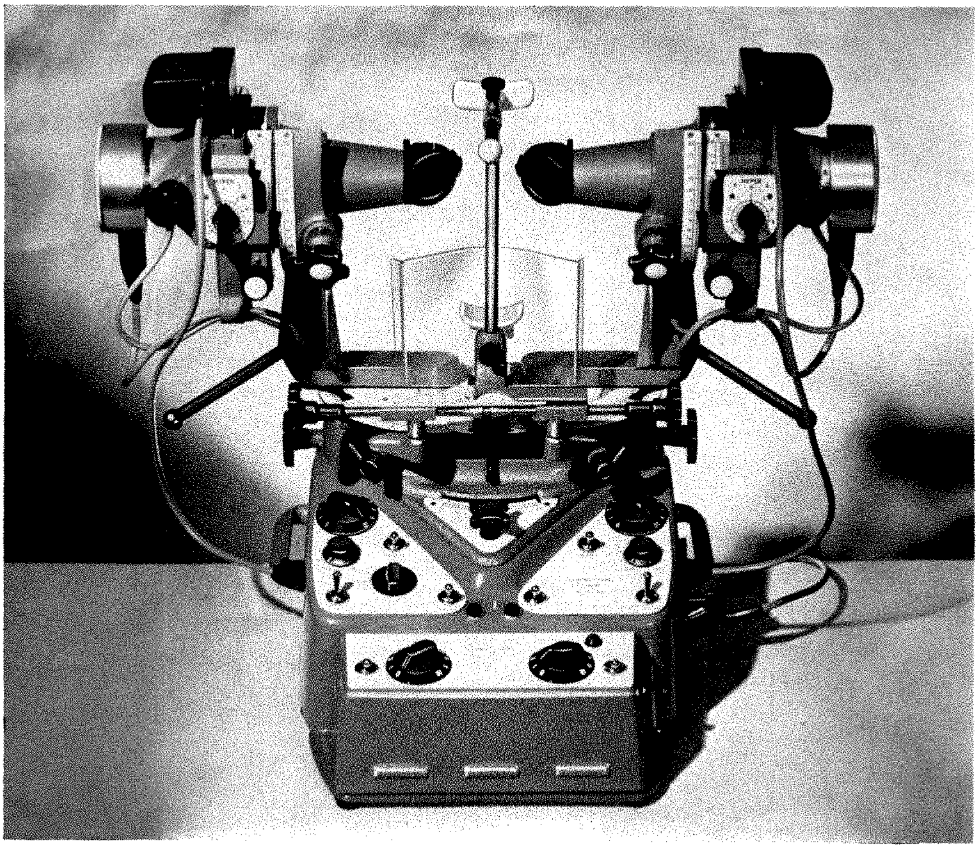

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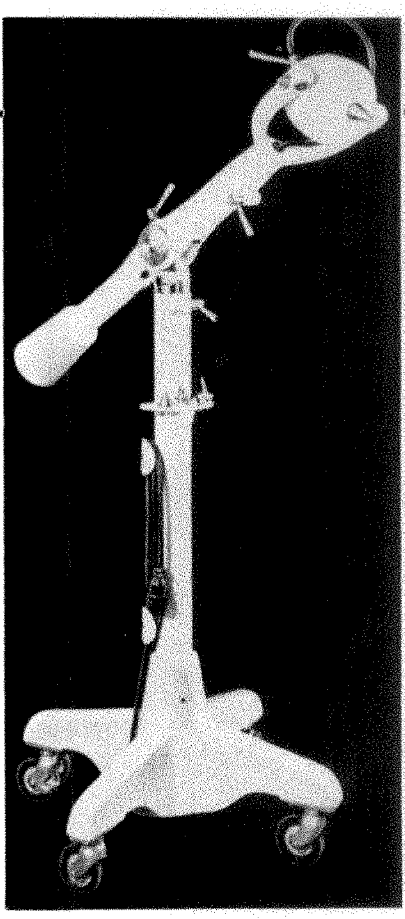

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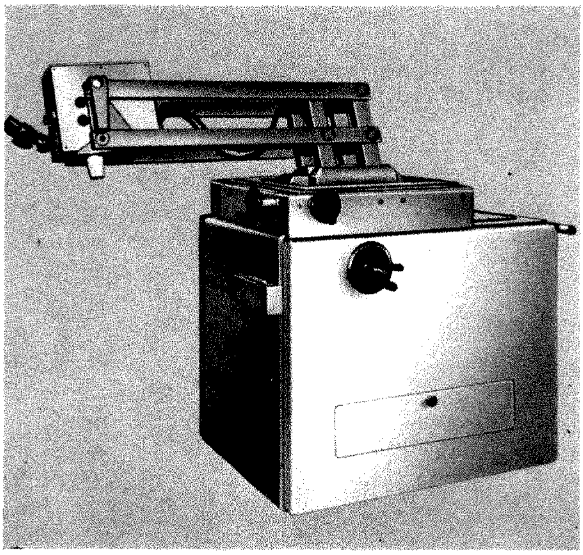

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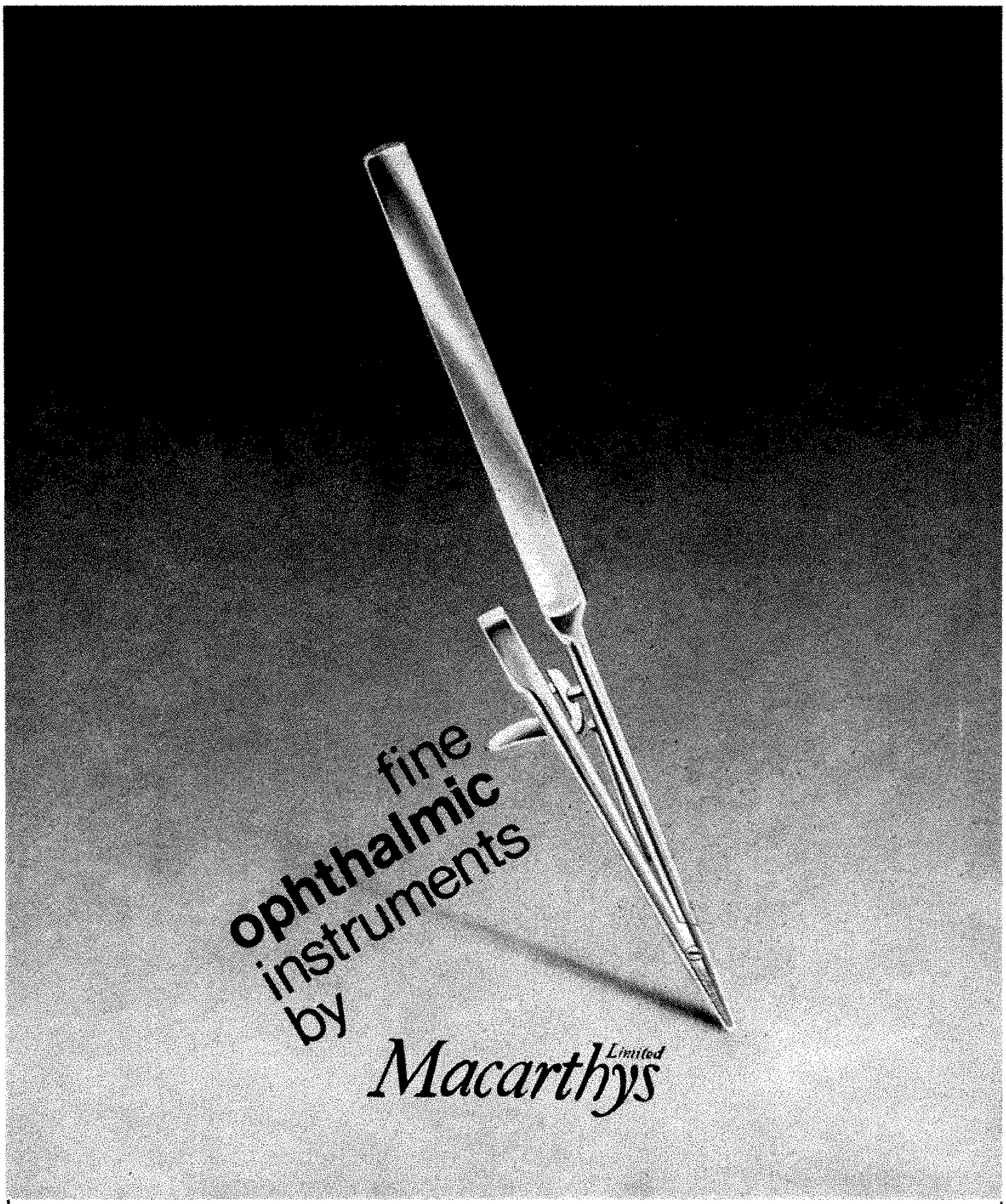

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Communications

Corneal granular dystrophy

A light and electron microscopical study of its recurrence in a graft

R. C. TRIPATHI AND A. GARNER

Department of Pathology, Institute of Ophthalmology, University of London

Histochemical evidence suggests that the amorphous stromal deposits of corneal granular dystrophy are composed essentially of a non-collagenous protein or polypeptide complex, the precise nature of which, however, is unknown (Seitz and Goslar, 1963; Garner, 1969). Electron microscopy fortunately enables a further dimension of this material to be studied, and the present report gives the findings in a corneal disc removed from an established case of granular dystrophy during a repeat keratoplasty after the recurrence of the disorder in the original graft.

Material and methods

Two specimens were available: the first was a full-thickness disc obtained when the patient, a female aged 33 years, was subjected to penetrating keratoplasty of the right eye, and the second was a partial-thickness disc removed some 10 years later from the same eye after the development of superficially-placed opacities in the donor tissue.

The original specimen had been fixed in 10 per cent. formol-saline and embedded in paraffin wax for histological sectioning at the Queen Victoria Hospital, East Grinstead; the second was received in buffered glutaraldehyde at the Institute of Ophthalmology, London, where it was divided into two parts, for light and electron microscope study respectively. The portion selected for electron microscopy was post-fixed in Zetterqvist's osmium tetroxide and embedded in Araldite, and selected areas were sectioned at 500 to 800 Å on an LKB ultratome III. Sections, stained with uranyl acetate followed by either lead citrate or phosphotungstic acid, were then examined with an AEI-EM6 electron microscope.

The remaining portion of the disc was processed for light microscopy, sectioned at a thickness of 5 μ, and, in addition to routine staining, subjected to specific staining for protein and amino-acid groups as previously described (Garner, 1969). Sections from the original specimen were similarly stained.

Results

LIGHT MICROSCOPY

The tissue removed at the time of the first graft operation consisted of a full-thickness disc of cornea from which the surface epithelium had been artificially detached. Bowman's membrane was completely destroyed and the stroma at all levels included widespread focal deposits of an amorphous eosinophilic material. Descemet's membrane was intact and

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there was no apparent endothelial abnormality. The stromal deposits stained red by the Masson trichrome procedure (Fig. 1), but gave no reaction with either periodic acid-Schiff or acid polysaccharide staining methods; they gave positive reactions for protein and were shown to contain tyrosine, arginine, tryptophan, and sulphur-containing amino-acids.

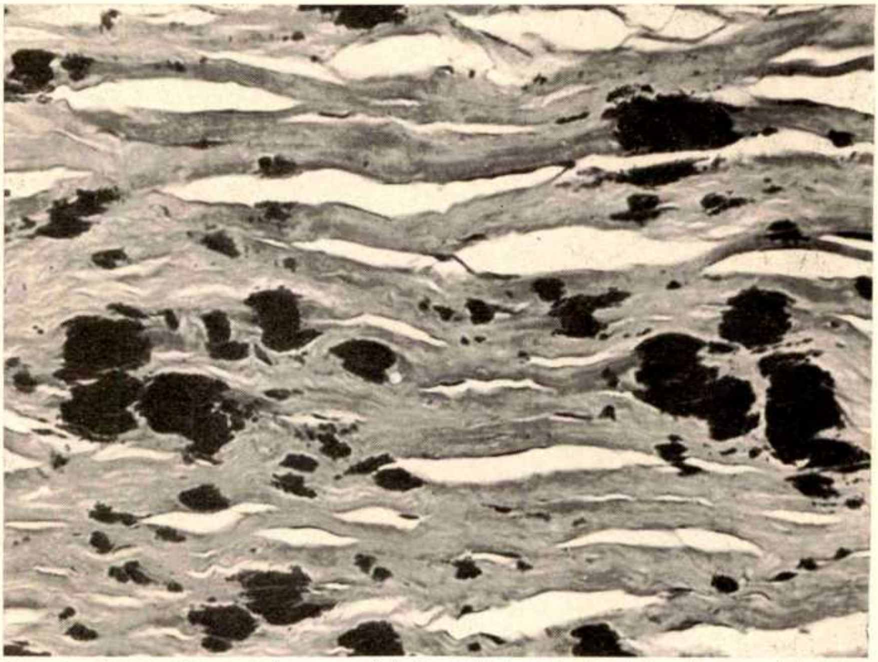

FIG. 1 *Section of corneal disc removed during initial graft operation, showing red-staining granular deposits distributed throughout the substantia propria. Masson trichrome* ×340

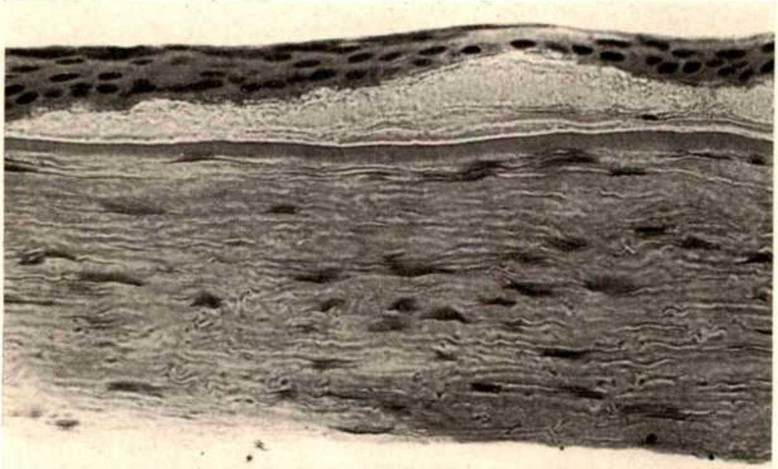

FIG. 2 *Lamellar disc of donor cornea removed at second keratoplasty, showing accumulation of granular material between Bowman's membrane and the epithelium. Haematoxylin and eosin* ×225

The lamellar disc removed at the second operation was made up mainly of donor tissue with a small margin of host cornea at the periphery. The stroma of the donor cornea was apparently normal and Bowman's membrane was intact, but between the latter and the epithelium there was a layer of amorphous material (Figs 2 to 4) comparable to that seen in the stroma of the original specimen. Similar deposits were present in the stroma of the host tissue present at the edges of the donor tissue. Apart from an essentially negative response to Masson's trichrome stain, a finding almost certainly due to prolonged fixation in glutaraldehyde, the staining reactions of the tissue deposits in the second specimen were identical to those in the first. Amyloid was not demonstrable in either.

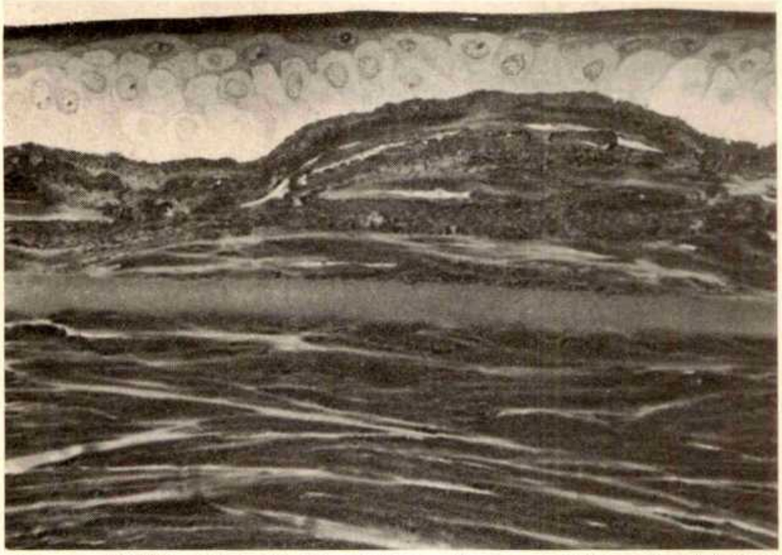

FIG. 3 *Araldite section of the recurrence, showing granular material between Bowman's membrane and the epithelium deposited within a collagenous matrix. Toluidine blue* ×360

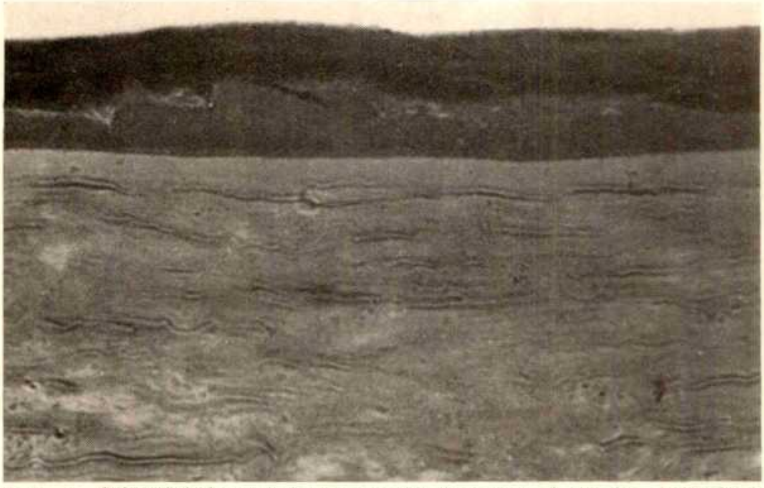

FIG. 4 *Subepithelial material stains strongly for protein, as also does the overlying epithelium; the stroma and Bowman's membrane are less intensely stained. Coupled tetrazonium* ×225

Details of the staining reactions in the two specimens are presented in the Table.

Table *Histological staining reactions of the corneal lesions*

Method	*Reaction of granular deposits*	
	Original specimen	*Recurrence*
Haematoxylin and eosin	Eosinophilic	Eosinophilic (uneven)
Masson trichrome	Red	Unstained
Wilder silver	+	+
Birefringence	—	—
Periodic acid-Schiff	—	—
Alcian blue (pH 2·5)	—	—
Congo red	—	—
Methyl violet	Orthochromatic	Orthochromatic
Thioflavine-T fluorescence	—	—
Coupled tetrazonium for protein	++	++
Ninhydrin-Schiff for protein-bound amino groups	—	—
Hydroxynaphthaldehyde for protein-bound amino groups	+	±
Diazotization-coupling for tyrosine	++	+
p-Dimethylaminobenzaldehyde for tryptophan	±	±
Sakaguchi for arginine	+	+
Dihydroxy-dinaphthyl-disulphide (DDD) for sulphydryl groups	+	++
Thioglycollate—DDD for sulphydryl and disulphide groups	++	++

ELECTRON MICROSCOPY

The most striking feature was the presence, between Bowman's membrane and the epithelium of the donor cornea, of electron dense structures which at low resolution had a superficially crystalline appearance (Figs 5 and 6). Presenting as an agglomeration of variably sized rod-shaped or trapezoid profiles, and ranging in width from 100 to 500 mμ, the deposits were shown at higher magnification to be composed of an amorphous material without evidence of a fibrillar or filamentous arrangement (Fig. 7).

Between the deposits there was a network of randomly orientated collagen fibrils together with some finer filaments (Fig. 8) such as are commonly found in corneal scar tissue in a variety of conditions (Rice, Ashton, Jay, and Blach, 1968), but apart from their spatial proximity there was nothing to suggest that the amorphous deposits were a product of these collagenous elements. Associated with the collagen fibrils was a small number of fibroblasts, the majority of which appeared entirely normal (Fig. 9), although occasional cells showed some vacuolation of their cytoplasm.

The overlying epithelium was apparently normal, showing no evidence of secretory activity or of degeneration (Fig. 10), while both Bowman's membrane and the underlying superficial lamellae of the substantia propria were composed of mature collagen with complete absence of the abnormal deposits present in the subepithelial zone.

Discussion

Of the few published reports of the ultrastructure of corneal granular dystrophy (McTigue, 1965, 1967; Sornson, 1965; Kuwahara, Akiya, and Obazawa, 1967; Matsuo, Fujiwara and Ofuchi, 1967; Teng, 1967), only Matsuo and his colleagues present findings analogous to

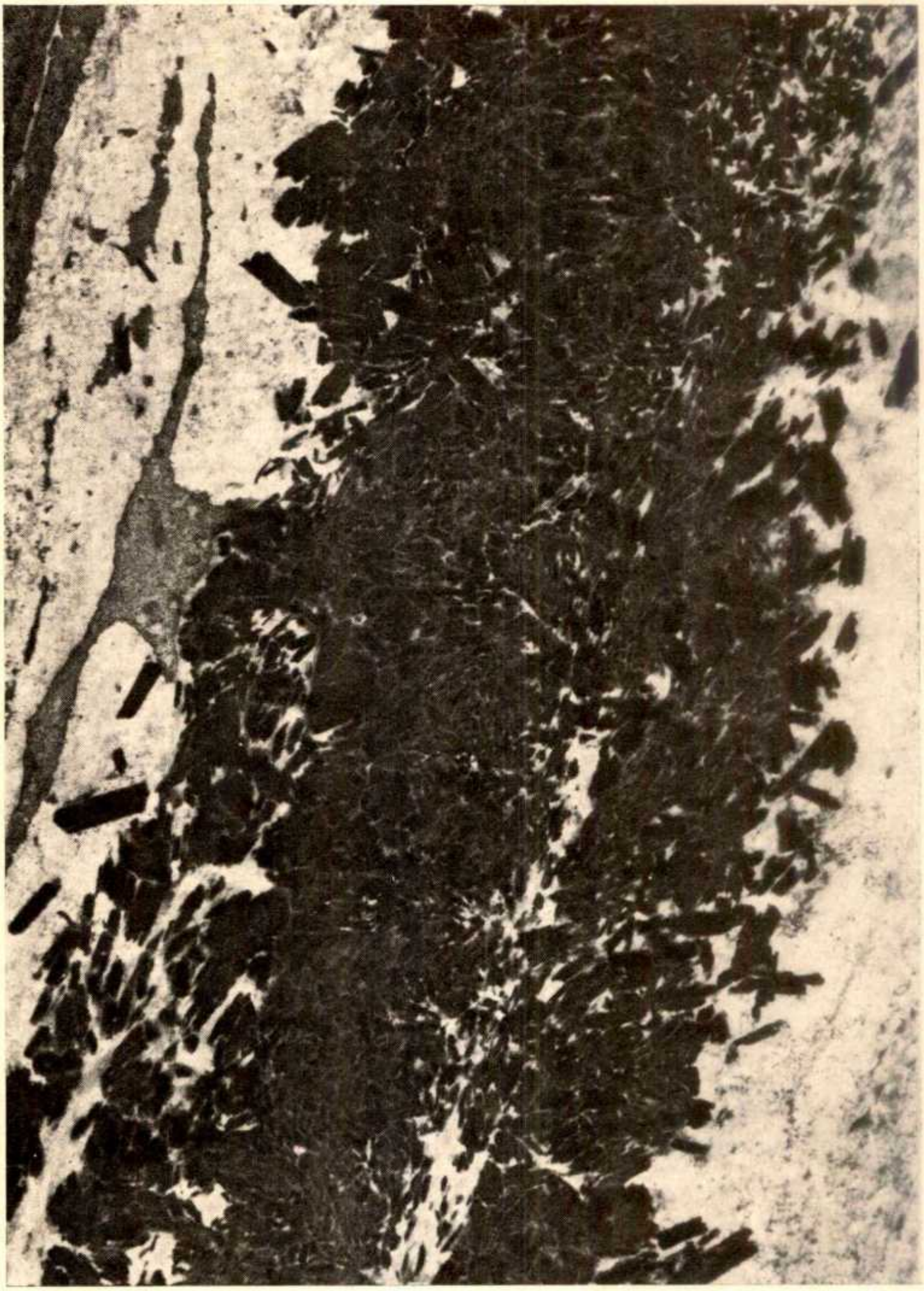

FIG. 5 *Survey electron micrograph of recurrence, showing subepithelial deposition of electron dense trapezoid and rod-shaped "crystals". Uranyl acetate–lead citrate* ×10,000

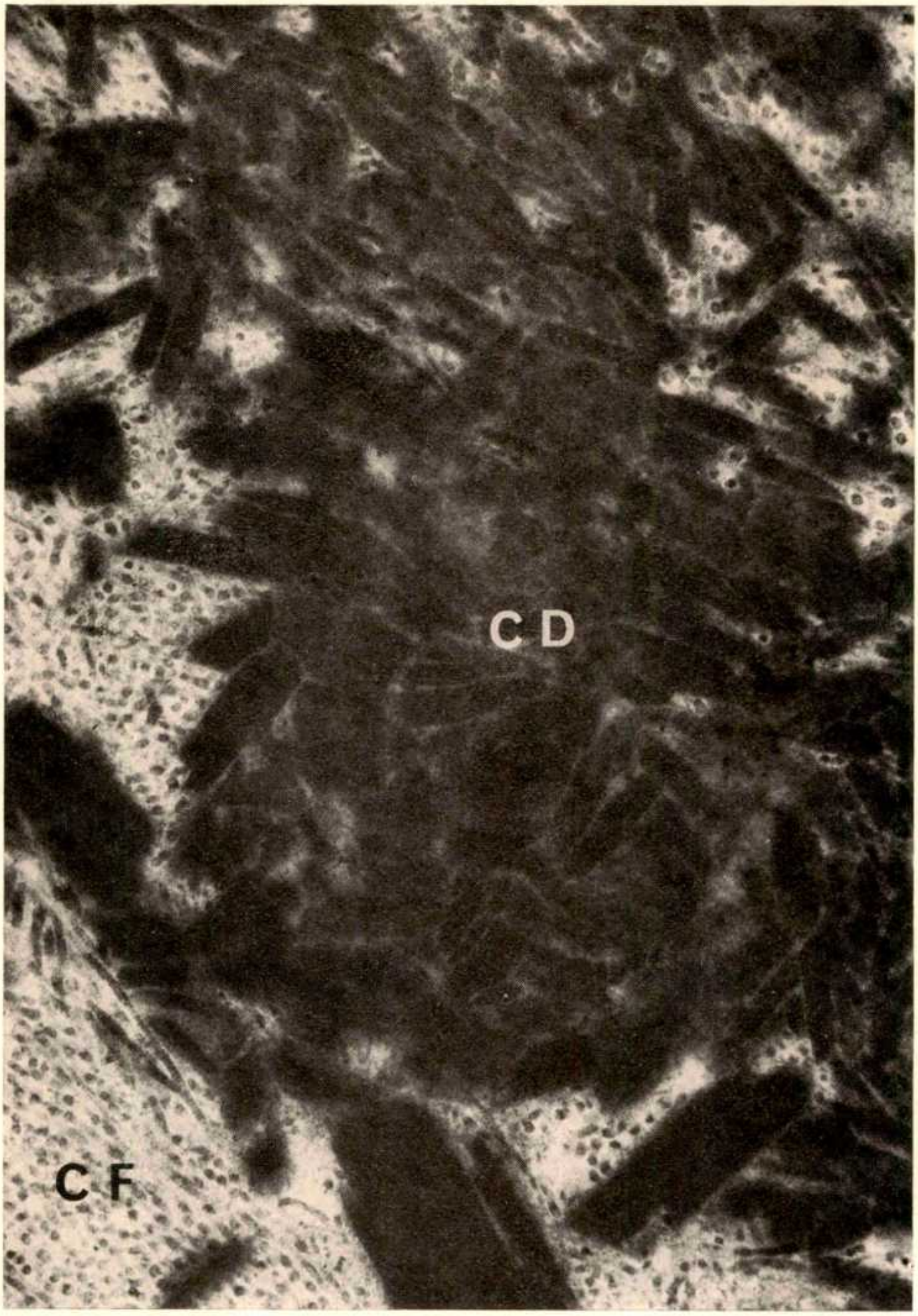

FIG. 6 *"Crystalline" deposits (CD) lie within a matrix of randomly orientated mature collagen fibrils (CF) Uranyl acetate–lead citrate. Electron micrograph* ×50,000

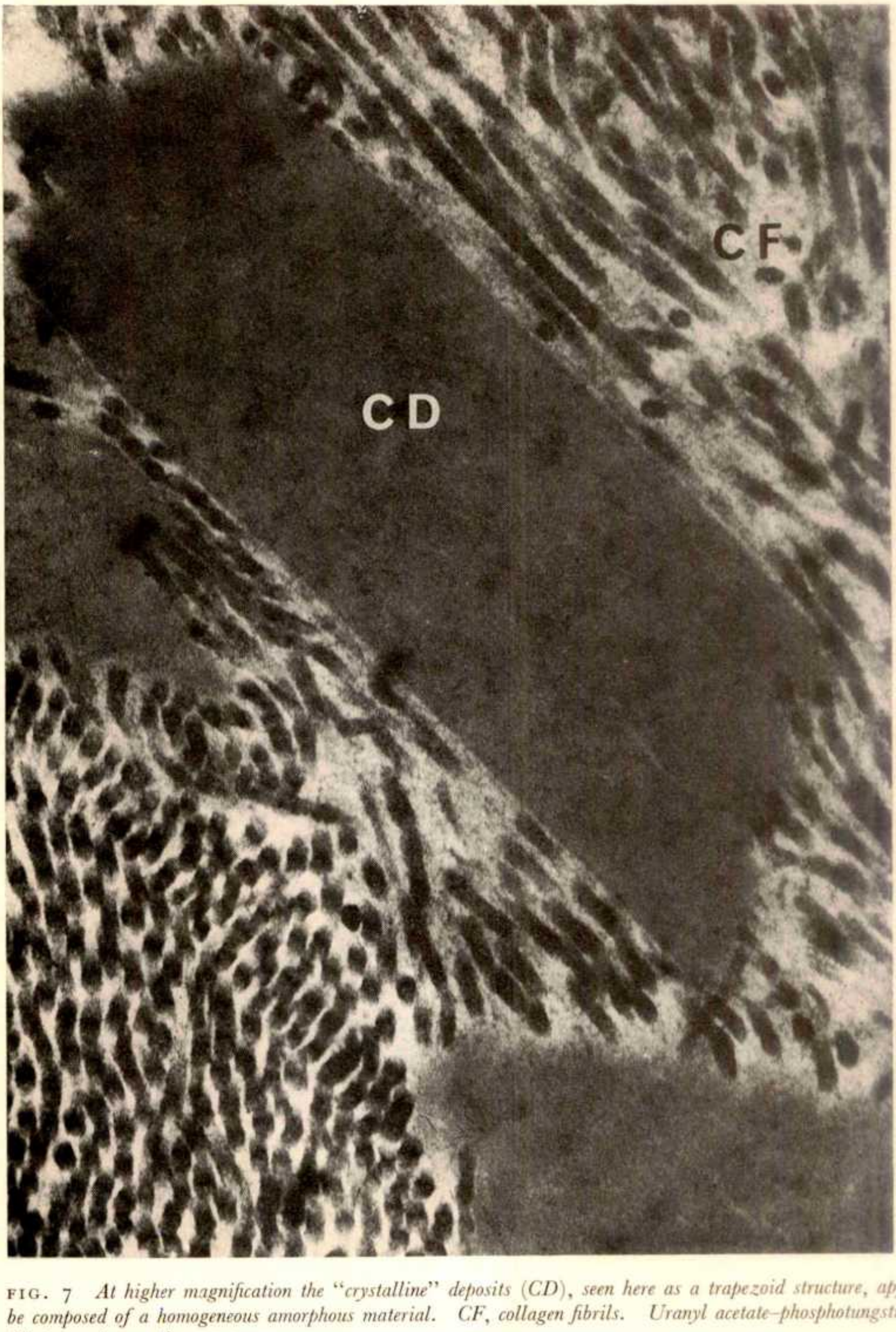

FIG. 7 *At higher magnification the "crystalline" deposits (CD), seen here as a trapezoid structure, appear to be composed of a homogeneous amorphous material. CF, collagen fibrils. Uranyl acetate–phosphotungstic acid. Electron micrograph* ×97,500

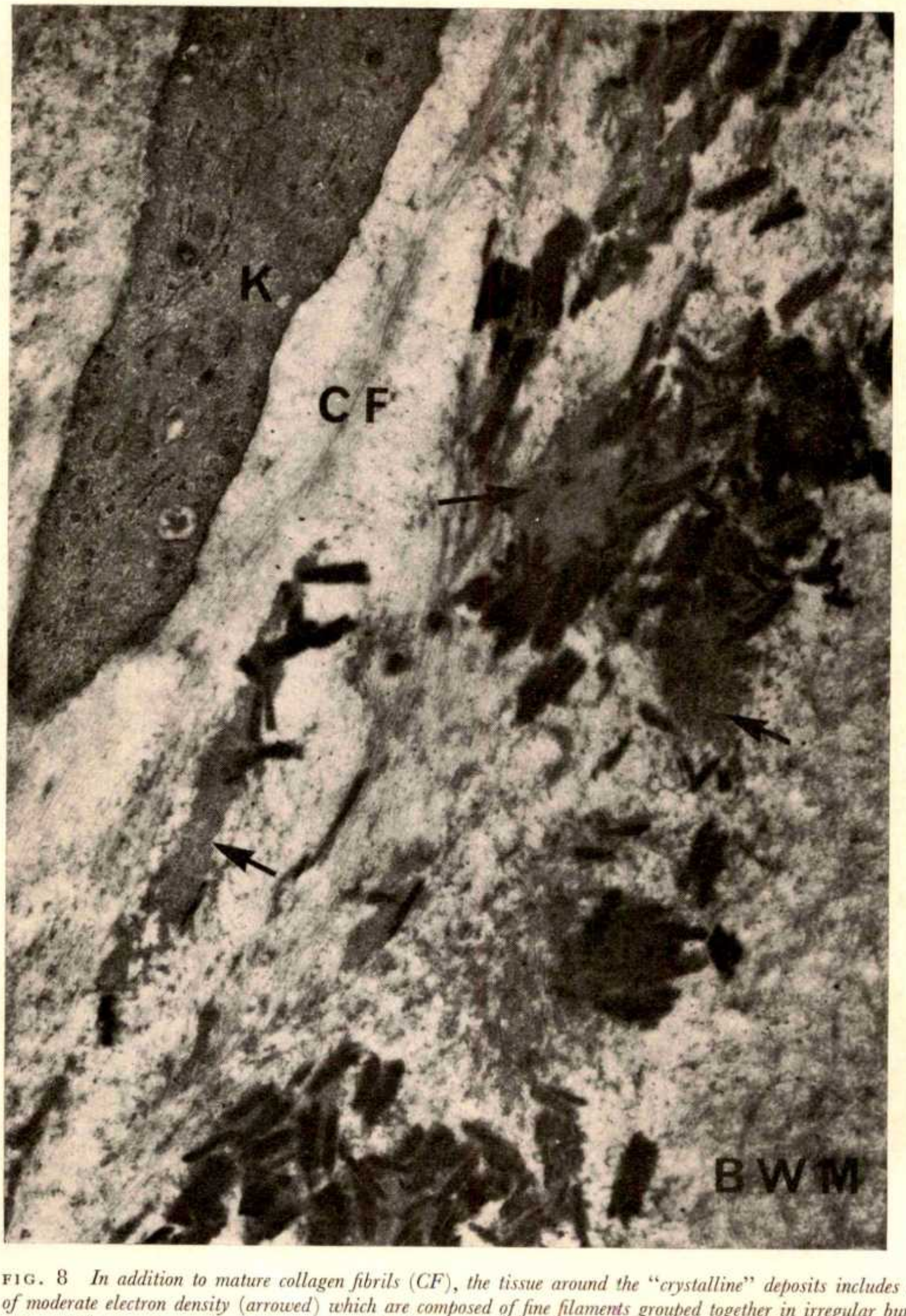

FIG. 8 *In addition to mature collagen fibrils (CF), the tissue around the "crystalline" deposits includes areas of moderate electron density (arrowed) which are composed of fine filaments grouped together in irregular bundles. The cytoplasm of an adjacent keratocyte (K) shows no abnormality. BWM, Bowman's membrane. Uranyl acetate–lead citrate. Electron micrograph* ×20,000

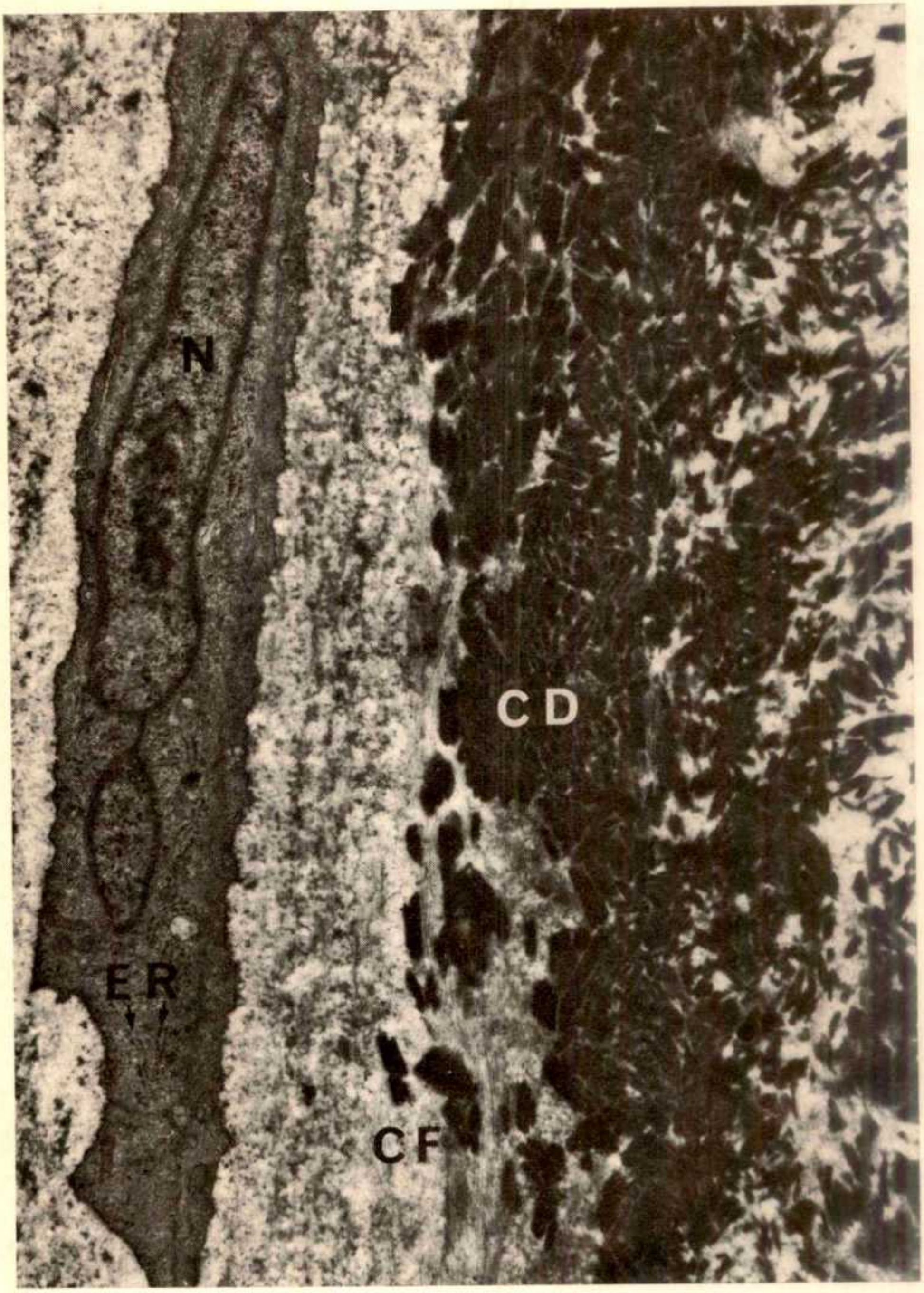

FIG. 9 *Most of the keratocytes associated with the "crystalline" deposits (CD) showed no obvious sign of degenerative change. N, nucleus; ER, endoplasmic reticulum; CF, collagen fibrils. Uranyl acetate–lead citrate. Electron micrograph* ×15,000

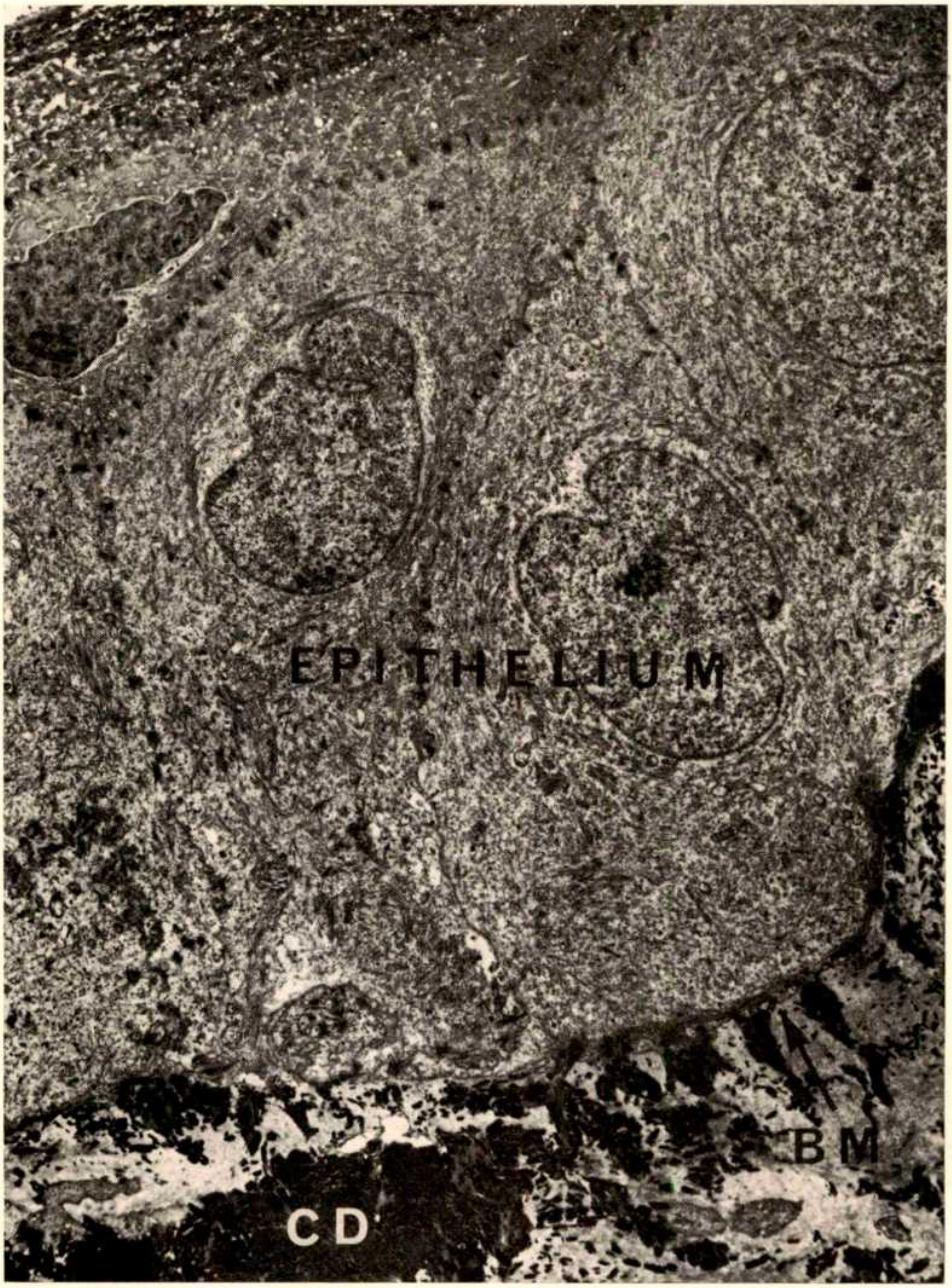

FIG. 10 *Survey electron micrograph, showing that while the "crystalline" deposits (CD) abut on to the basement membrane (BM) of the corneal epithelium, the cells themselves appear normal. Uranyl acetate–lead citrate. Approx.* ×2,300

our own. (Kuwahara's group comment on the presence of rod-shaped structures but do not provide any pictorial evidence, so that their contribution cannot be assessed.) Nevertheless, there would seem to be good reason to regard these "crystalline" structures as characteristic of this disorder, since study of another case (Case 1 of the series reported by Garner, 1969), in which the cornea had previously been embedded in paraffin wax for histological examination, has shown the same type of deposit within the stroma (Fig. 11).

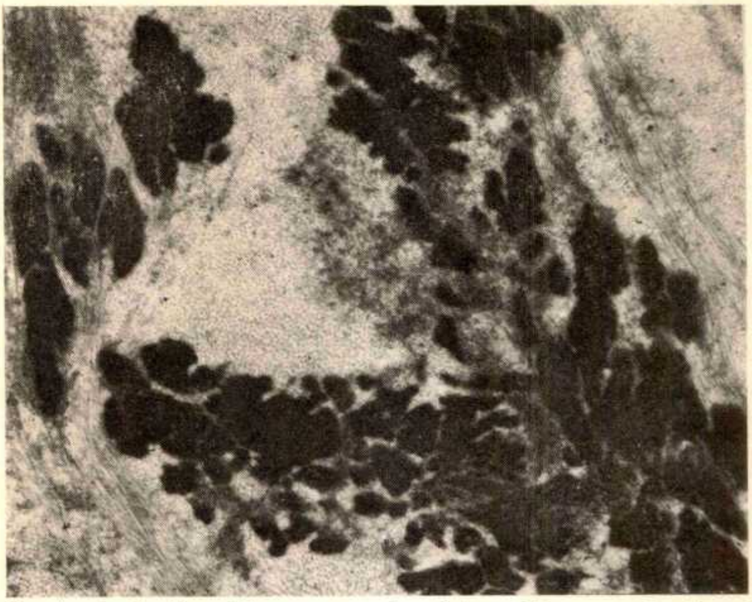

FIG. 11 *Electron micrograph of stromal deposits in typical granular dystrophy. The material was obtained by de-paraffinizing tissue previously embedded for histological examination. Despite inadequate processing for electron microscopy, the "crystalline" nature of the deposits is still readily seen. Formol-saline fixation. Post-fixed in osmium tetroxide. Uranyl acetate–lead citrate.* × 19,500

On the basis of positive congo red staining, Matsuo and others (1967) interpreted these structures as being amyloid but, since this reaction can be regarded as diagnostic only if the deposits so stained exhibit green dichroism when viewed between crossed Nicol prisms (Missmahl, 1957), their conclusion is not necessarily valid, especially as there is no record that this step was carried out. Furthermore, in neither their study nor ours did the electron microscopic appearances of the deposits bear any resemblance to the characteristic fibrils described in other forms of amyloidosis (Cohen, 1967). A non-fibrillar component or precursor of amyloid has recently been described, however, which might be expected, at electron microscope resolutions comparable to those obtainable in our study, to present as an amorphous or finely granular moiety (Bladen, Nylen, and Glenner, 1966; Hirschl, 1969), and the possibility that the tissue deposits in granular dystrophy may be related in some way to this component cannot therefore be discounted.

While the histochemical and ultrastructural evidence in the present case has failed to identify the material in question, it cannot exclude the possibility that it may be related to amyloid, but it is strongly against an origin from collagen, either as a degenerative product (Franceschetti and Babel, 1951) or as an incomplete precursor (Teng, 1967). The composition of collagen, and for that matter of reticulin, is incompatible with the demonstrable amino-acid content of the tissue deposits in granular dystrophy, as has already been observed (Garner, 1969). Moreover, the ultrastructure of the deposits is quite unlike that described for immature collagen or reticulin (Melcher, 1966). That reticulin or some related incomplete form of collagen is also present is not denied. Indeed the study by Teng (1967) showing large numbers of fine filaments within the lesions, our own finding of fine fibrils similar to those seen in scar tissue occurring in other forms of corneal disease

(Rice and others, 1968), and the demonstration of argyrophilic fibres by light microscopy make it extremely likely. It is, however, our impression that these components which are probably non-specific are of secondary importance in the pathogenesis of the disorder.

On account of some histochemical resemblance to keratin or keratohyaline, the suggestion has been made that the granular deposits might possibly derive from abnormal squamous epithelium (Garner, 1969), but this finds no support in the present study. Rather the absence of any discernible epithelial abnormality in the donor corneal graft points to the deposits being a product of host keratocytes which had invaded the subepithelial zone to form an anterior graft membrane of the type not uncommonly seen in unsuccessful keratoplasties (Winter, 1969). It is to be noted that only a minority of the keratocytes situated in and around the subepithelial deposits showed any sign of degenerative change, which suggests that, while cellular degeneration may occur as Sornson (1965) and Teng (1967) have stressed, it is probably not essential for the elaboration of the granular material.

Summary

Following the recurrence of opacities in the grafted cornea in the eye of a female patient suffering from heredofamilial granular dystrophy, a repeat keratoplasty was performed and the excised lamellar disc of opaque tissue was submitted for histochemical and electron microscopical study. This revealed accumulations of a protein substance between Bowman's membrane and the epithelium which ultrastructurally presented as amorphous material, grouped in bizarre rod-shaped and trapezoid masses, and deposited within a collagenous environment. Its possible nature is discussed.

It is a pleasure to acknowledge our indebtedness to Mr. A. Werb of the Corneo-Plastic Unit at the Queen Victoria Hospital, East Grinstead, for allowing us to publish this case, and to Major-General A. Sachs for kindly providing material from the original corneal specimen. We would also thank Prof. N. Ashton for his invaluable comments and advice, Mr. A. McNeil and Miss Susan Legg for technical assistance, and Miss Ruth Mason for secretarial assistance.

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Dominantly inherited drusen of Bruch's membrane

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Hyaline bodies may be found in the optic disc and in several parts of the retina as a non-specific finding (Wolter, 1959). The term drusen ("colloid bodies") is usually reserved for large hyaline bodies of the optic disc and Bruch's membrane.

Lorentzen (1966), postulated that drusen of the optic disc had an irregular dominant pattern of inheritance after an examination of the relatives of 49 affected individuals.

Drusen of Bruch's membrane are found in several degenerative conditions and systemic diseases and are often a senile manifestation (Duke-Elder, 1967). Not infrequently, however, they are the result of a primary hereditary dystrophy, usually transmitted as a regular dominant trait.

In spite of their common designation, which is based on the ophthalmoscopic appearance, the histochemical properties of drusen of the optic disc and of Bruch's membrane are somewhat different (Seitz and Kersting, 1962). This is understandable as the former consist of degenerative products of the nerve fibres, and the latter of degenerative products of the retinal pigment epithelium (Seitz, 1968).

Hereditary drusen of Bruch's membrane are known by a variety of names such as Tay's central guttate choroiditis, Holthouse-Batten's superficial chorioretinitis, Doyne's honeycomb choroiditis, and malattia leventinese. Franceschetti, François, and Babel (1963) regard hereditary drusen of Bruch's membrane as a single entity, but also recognize the four different types mentioned above; this leads to much confusion. With Waardenburg (1948), Forni and Babel (1962), Franceschetti and others (1963), Krill and Klien (1965), and Duke-Elder (1967), we think that all dominantly inherited drusen of Bruch's membrane constitute one clinical entity. The three cases described by Hutchinson and Tay (1875) and the one case reported by Holthouse and Batten (1897) do not represent separate entities, and the differential diagnosis between Doyne's honeycomb choroiditis (Doyne, 1899, 1910) and malattia leventinese (Vogt, 1925; Klainguti, 1932) is impossible, as the ophthalmoscopic, functional, histological, and hereditary properties are identical in both conditions (Treacher Collins, 1913; Forni and Babel, 1962; Pearce, 1968). Drusen of Bruch's membrane can thus be divided into the two following categories: degenerative and hereditary.

The hereditary drusen constitute one of the dystrophies of the central retina of which there are several distinct types, including Stargardt's disease, vitelliform dystrophy of the fovea, fundus flavimaculatus, and reticular dystrophy of the pigment epithelium (Sjögren). For this clinical entity we suggest the name "dominant drusen of Bruch's membrane".

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The clinical picture of dominant drusen is variable. All sizes of drusen from small (Fig. 1) to large (Fig. 2) have been described (Fuchs, 1956). This dystrophy usually affects both eyes symmetrically and develops between the ages of 20 and 30 years with a few small round white drusen appearing at both posterior poles. These usually increase in number and later in size until late middle age, when the posterior pole is covered with white spots, which may show a mosaic, though the typical honeycomb appearance described by Doyne is often absent. The spots then coalesce and the overlying retina becomes thin and atrophic, while pigmentation and choroidal atrophy become apparent. As a complication retinal haemorrhages may occur. The finding of white colloid bodies on the nasal side of the disc (Fig. 3) may be regarded as virtually pathognomonic of

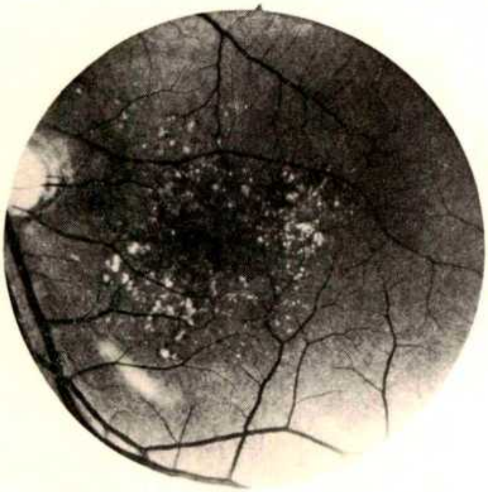

FIG. 1 *Small drusen of Bruch's membrane*

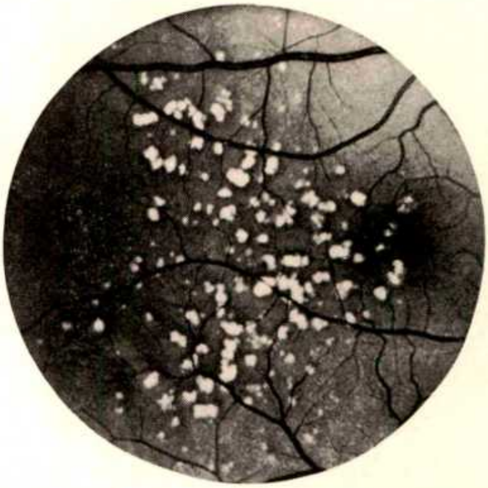

FIG. 2 *Rather large drusen of Bruch's membrane*

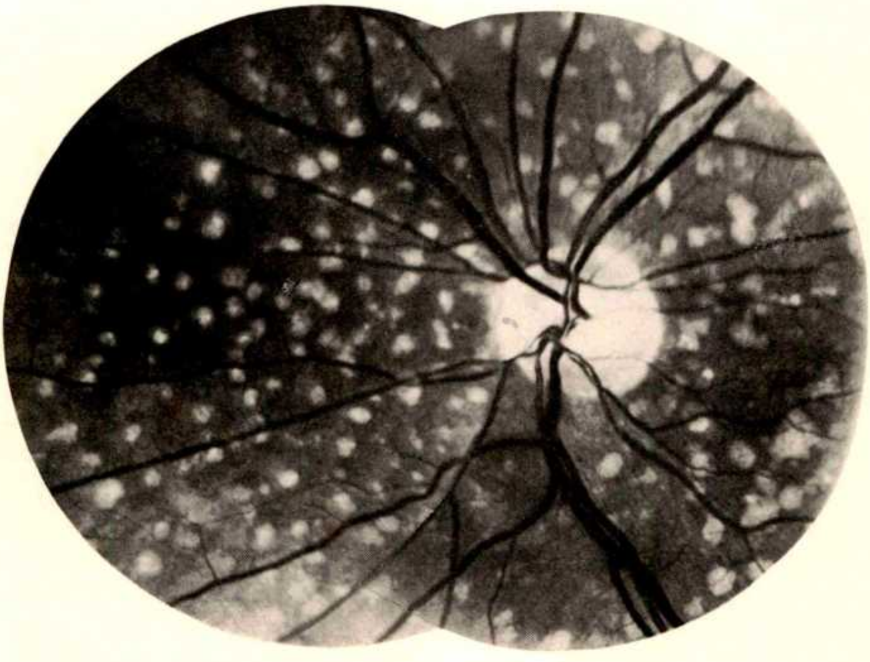

FIG. 3 *Drusen surrounding the optic disc*

dominant drusen. In advanced cases almost rectangular patches surrounding the optic disc are a characteristic feature.

The purpose of this paper is to present two families, each with a characteristic ophthalmoscopic pattern. Individuals are not usually affected ophthalmoscopically by this dystrophy before the age of 20 years, but we found dominant drusen in a pair of identical twins and in two boys aged 12 and 14 years.

The two families included ten affected individuals and, apart from two cases reported by Waardenburg (1948), no other cases have been described in the Netherlands.

Case histories

FAMILY 1 (Fig. 4)

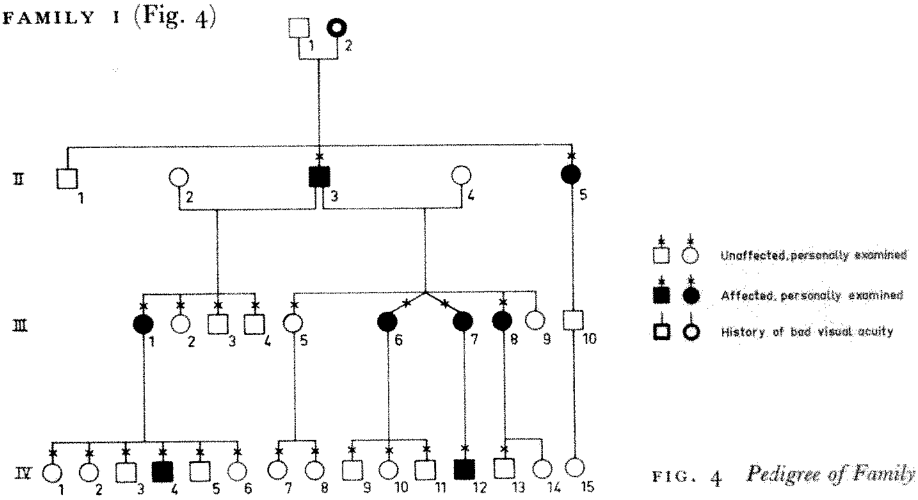
II
III
IV
Unaffected, personally examined
Affected, personally examined
History of bad visual acuity

FIG. 4 *Pedigree of Family 1*

Case II.3 This man had extensive central chorioretinal atrophy of both eyes in the last years of his life. Visual acuity had been diminished to counting fingers.

Case II.5, a 79-year-old woman. The posterior poles of both eyes show confluent drusen in the papillo-foveal region. There is some pigmentation. Despite her age, the visual acuity is 0·4, with +1·25 D sph., +0·25 D cyl., axis 180°, in the right eye, and 0·5, with +0·75 D sph., +1·5 D cyl., axis 180°, in the left.

Case III.1, a 59-year-old woman. Visual acuity in both eyes is 1·0, with +0·25 D sph. Both posterior poles show colloid bodies. Between these drusen a fine granular pigmentation is present. Most drusen are situated in the parafoveal region. The ocular media, discs, retinal vessels, and retinal peripheries are normal. The visual fields are full and dark adaptation is unaffected. The anomaloscope of Nagel and the Hardy-Rand-Rittler (HRR) test indicate normal colour vision.

Case III.6, a 35-year-old woman, one of identical twins, has some metamorphopsia in the right eye (Amsler test). Visual acuity in both eyes is 0·9, with +0·25 D sph. in the right eye, and +0·50 D sph. in the left. The media are normal. Both posterior poles show numerous fine round, white and yellowish-brown drusen (Fig. 5*a*, *b*, overleaf). Some slight pigmentation is visible between the colloid bodies. The diameter of the drusen decreases from the centre of the fovea to the perifoveal area. The drusen are located in the deeper retinal layers beneath the retinal vessels. Retinal peripheries, vessels, and discs are normal. Peripheral visual fields are full but there are small relative central scotomata of about 5° in both eyes. The HRR test indicates a slight red-green dyschromatopsia, while Nagel's anomaloscope reveals a slightly diminished sensitivity to red in both eyes. Dark adaptation, electroretinogram (ERG), and electro-oculogram (EOG) are normal.

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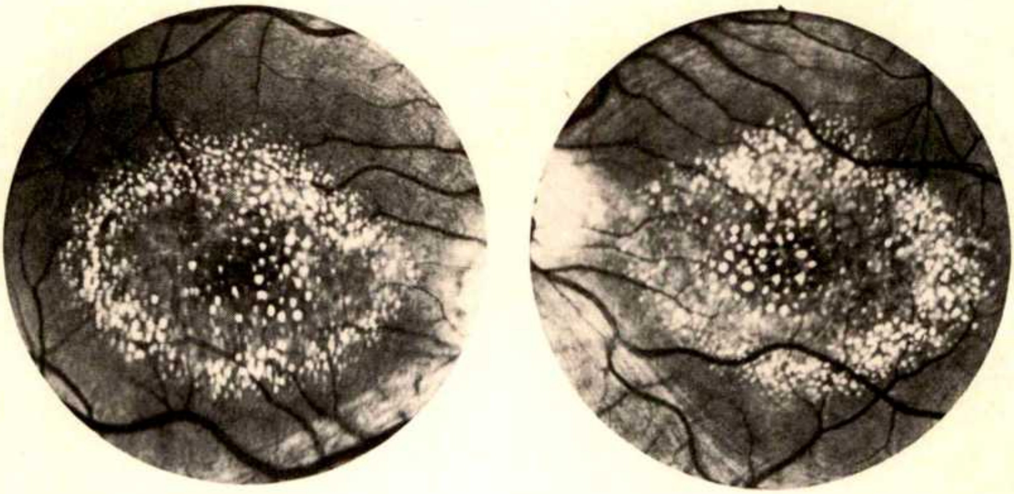

(5a) (5b)

FIG. 5 *Right* (a) *and left* (b) *posterior poles of one of the identical twins* (*III*-6, *Family* 1)

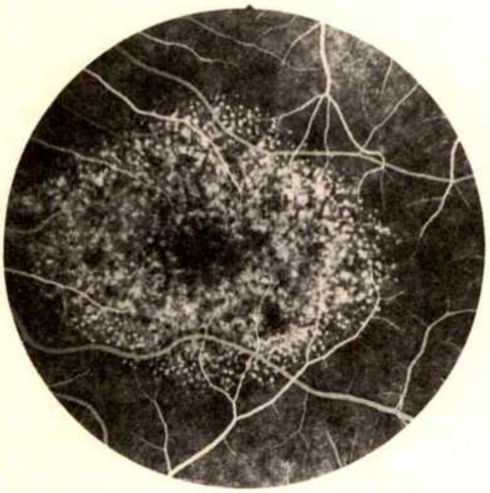

FIG. 6 *Fluorescein fundus photograph of left eye of III*-6, *Family* 1 (*cf. Fig.* 5b)

General physical examination and routine laboratory studies reveal no abnormalities. Total lipid, triglycerides, cholesterol, lipo-proteins, and protein spectra are all normal. Fluorescein angiography (Fig. 6) shows fluorescence in the arterial phase, increasing in the venous phase. The central drusen show confluence while the perifoveal drusen remain solitary. There are more defects visible in the pigment epithelium than with normal ophthalmoscopy. The fluorescent areas persist with no change in size for 12 minutes beyond the venous phase.

Case III.7, the other identical twin, has a fundus almost identical to that of her sister (Fig. 7*a*, *b*), but with somewhat less drusen in the centre of the retina. The retinal functional tests give almost exactly the same results as in her sister: a small relative scotoma, some diminished sensitivity to red, normal dark adaptation, and normal ERG and EOG. There is some metamorphopsia in the right eye and the visual acuity is 0·9 in both eyes (emmetropic). The media are normal.

Case III.8, a 33-year-old woman, has a visual acuity of 0·6, with +1·25 D sph., in both eyes. A coralliform cataract is present while the corneae are normal. The central retinae reveal a very fine granular pigmentation while, particularly in the parafoveal region, there are tiny round drusen. The retinal peripheries, vessels, and discs are normal. The visual fields and colour vision are unaffected.

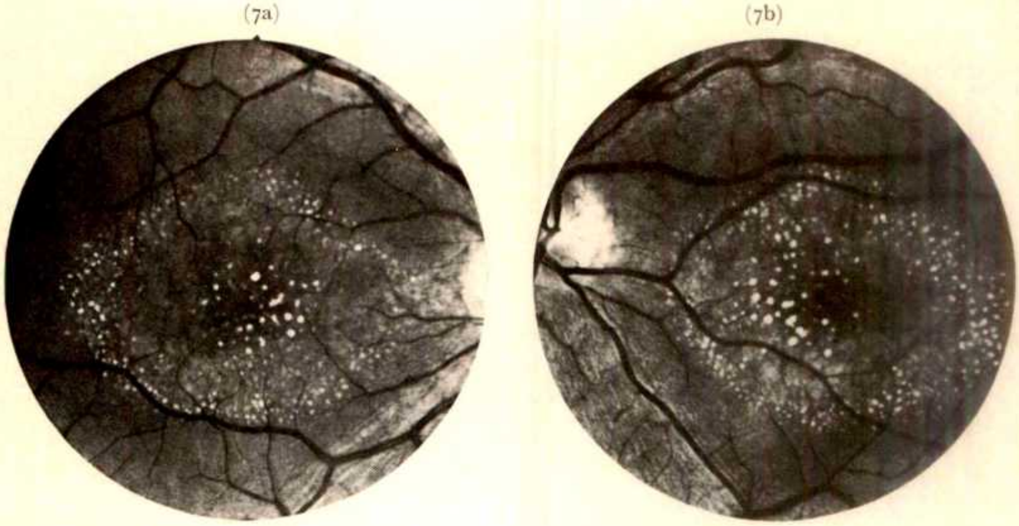

FIG. 7 *Right* (a) *and left* (b) *posterior poles of the other identical twin* (*III*-7, *Family* 1)

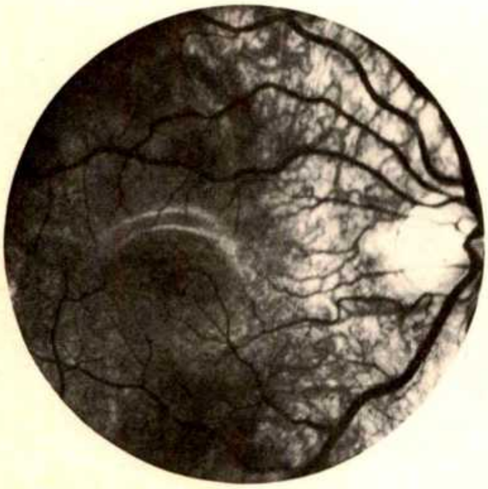

FIG. 8 *Drusen in posterior pole of a* 12-*year-old boy. Note that the drusen have a yellowish-brown colour* (*IV*-12, *Family* 1)

Case IV.4, a 14-year-old emmetropic boy, has a visual acuity of 0·9 in each eye. The foveal reflexes are normal but in the deeper retinal layers fine pigmentation and some yellowish-brown drusen are present. No further anomalies were found. The colour vision and visual fields are normal.

Case IV.12, a 12-year-old boy, has a visual acuity in both eyes of 1·0, with +0·50 D sph. There is no metamorphopsia (Amsler test). The reflexes of the fovea and foveola are normal, while there are some yellowish-brown drusen in the foveal area (Fig. 8). No further abnormalities are present. The visual fields and colour vision are normal.

FAMILY 2 (Fig. 9, overleaf)

Cases I.1 and 2 The parents died when II.4 was a young girl. Nothing is known about their visual acuity.

Case II.4, a 67-year-old woman, has increasing visual complaints. The visual acuity of both emmetropic eyes is now 0·6 having been 1·0 one year previously. Both eyes reveal many large drusen at the posterior poles (Fig. 10*a*, *b*), and also on the nasal side of the discs. Pigmentation and glistening reflexes are also seen. The discs, retinal vessels, and retinal peripheries are normal.

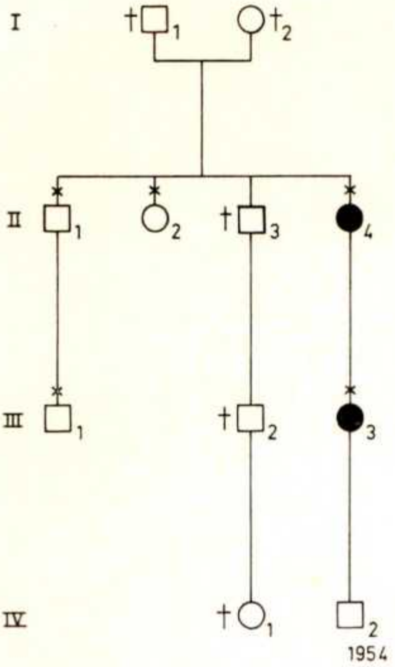

FIG. 9 *Pedigree of Family 2*

For key see Fig 4

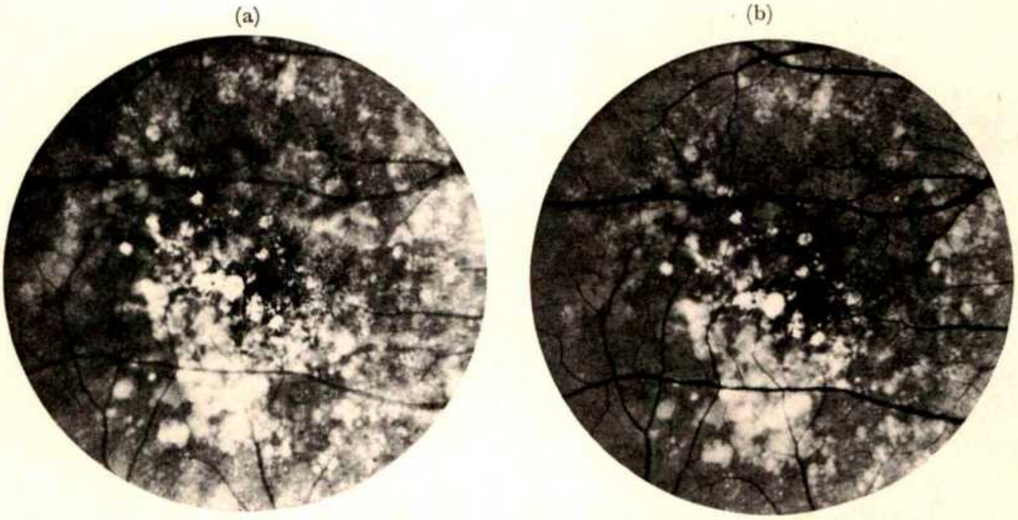
(a)
(b)

FIG. 10(a) *Panchromatic photograph of drusen in a 67-year-old woman (II-4, Family 2). There are more abnormal structures visible than on the orthochromatic film (Fig. 10b)*

FIG. 10(b) *Orthochromatic photograph of the same fundus as in Fig. 10a*

There is no metamorphopsia. The visual fields show relative central scotomata of about 8°. Some red-green as well as blue-yellow dyschromatopsia was found (HRR test and anomaloscope). Dark adaptation is slightly delayed, and the ERG shows subnormal scotopic and normal photopic values. The EOG is subnormal (right eye 165 per cent.; left eye 146 per cent.). General physical examination and routine laboratory tests revealed slightly disturbed liver function tests and hyperlipoidaemia.

Case III.3, a healthy 45-year-old woman, has no complaints. Visual acuity of 1·0 in the right eye, with +0·50 D sph., and 0·2 in the left eye, with +2 D sph., +0·75 D cyl., axis 180°. The lowered visual acuity in the left eye is due to amblyopia. The ocular media and intraocular pressure are normal. The posterior poles of both eyes display large drusen with a honeycomb appearance (Fig. 11). The vessels, discs, and retinal peripheries are normal, visual fields and colour vision are unaffected. The dark adaptation and the electroretinogram are normal; the electro-oculogram, however, is subnormal (right eye 155 per cent.; left eye 164 per cent.). The technique of recording the EOG and the calculation in percentage of the light peak/dark trough ratio has been described previously (Henkes, Denier van der Gon, van Marle, and Schreinemachers, 1968; Deutman, 1969).

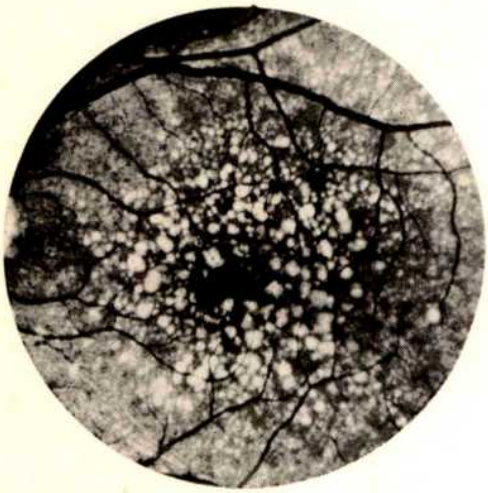

FIG. 11 *Drusen of Bruch's membrane arranged in a honeycomb pattern (III-3, Family 2)*

Comment

In Family 1 the dystrophy is inherited in a regular dominant manner. In Family 2 the inheritance is probably dominant; so far no affected person has been found in the third generation.

The drusen present in Family 1 are much smaller and less extensive than those in Family 2. These differences seem to be due to variability of expression. Differences in ophthalmoscopic appearance are more frequently found in other dominantly inherited retinal dystrophies, for example vitelliform dystrophy. In heterozygotes, modifying genes may have an important influence on the expressivity of the pathological gene.

The finding of drusen in identical twins and in the posterior poles of boys aged 12 and 14 years in Family 1 is most interesting. In the boys most of the drusen are not white, but of a yellowish-brown colour, indicating that the adjacent pigment cells are not yet completely destroyed. The youngest affected individuals hitherto described were over 20 years of age, but Evans (1950) described a family with "crystalline retinal degeneration" which included an 8-year-old affected girl. In all probability the family described by Evans is suffering from dominantly inherited drusen of Bruch's membrane. The finding of hereditary drusen in children indicates that this dystrophy should not be classified as an adult form of "heredodegeneration of the macula" (Falls, 1966).

The visual acuity remains normal for a long time but is usually diminished in advanced cases. Colour vision is normal until the fovea is affected, when a decreased sensitivity to red develops. When the destruction of the retina spreads an acquired blue-yellow dyschromatopsia may also be found. The peripheral visual fields remain full, while relative central scotomata develop, followed by absolute scotomata. Dark adaptation is usually normal. Pajtáš (1957), however, reported cases in which true hemeralopia was already present at the age of 14 years. The electroretinogram, being an overall response of the retina, is usually normal, even in advanced cases, but may become subnormal indicating diffuse damage to the neuroepithelium. Krill and Klien (1965) found only a delay in reaching an otherwise normal maximum *b*-wave.

Like the electroretinogram, the electro-oculogram is a test of the function of the whole retina. Drusen are situated on the inner side of Bruch's membrane and therefore tend to cause early disturbances in the pigment epithelium. In advanced cases a sub-normal electro-oculogram together with a normal electroretinogram and dark adaptation is frequently found, thus indicating the important relationship of the former to the integrity of the pigment epithelium. In other primary disturbances of the retinal pigment epithelium (e.g. in vitelliform dystrophy and fundus flavimaculatus), a pathological electro-oculogram together with a normal or slightly subnormal dark adaptation and electroretinogram is also found (Krill and Klien, 1965; Deutman, 1969). The more extensive affection of the second family is expressed in the subnormal electro-oculogram found in the two affected women.

Panchromatic films show more abnormal structures than do orthochromatic films (Fig. 10*a*, *b*). This means that the most extensive lesions are situated mainly in the deeper retinal layers (Craandijk and Aan de Kerk, 1969).

Fluorescein angiography shows the appearance of multiple fluorescent spots during the arterial phase the outlines of which correspond to the lesions noted on normal ophthalmoscopic examination, but more abnormal areas are visible. Most of the fluorescent areas persist beyond the venous phase with no change in size. There is no extravasation of dye; the visibility of the drusen is most probably due to a disturbance in the overlying pigment epithelium causing increased visibility of the underlying choroidal fluorescence (Ernest and Krill, 1966). The persistence of fluorescence after the dye has disappeared from the retinal vessels may be due to staining of the drusen (Rubinstein and Paton, 1966), but it may also be due to the normal capillary tissue fluid exchange, in which fluorescein permeates to the intercapillary space, which is visible in the case of pigment epithelium defects.

Histologically, drusen consist of round accumulations of hyaline within the pigment epithelium. These hyaline bodies are continuous with the inner layer of Bruch's membrane (Treacher Collins, 1913; Wolter, 1957, 1959; Forni and Babel, 1962; and others). In the initial stages the choroid and neuroepithelium are normal, but in advanced stages a considerable atrophy of these structures is found in the posterior pole of the eye. This dystrophy probably originates in an inborn error of metabolism, situated mainly in the retinal pigment epithelium. This can be concluded from the observations of Wolter (1957), who found two different developmental types of drusen:

(1) By accumulation of hyaline substance within slowly degenerating cells of the pigment epithelium;

(2) By extracellular deposition of hyaline substance beneath the pigment epithelium on Bruch's membrane.

Both types of drusen occur together and both finally result in the large hyaline formations on Bruch's membrane with the complete destruction of the adjacent pigment cells. As the choroid and the neuroepithelium are normal in early stages, we may assume that the pathogenesis in dominant drusen is a primary dystrophy of the cells of the pigment epithelium. Further support for this concept is given by Klien and Krill (1967) who found almost identical retinal function profiles and fluorescein patterns in cases of fundus flavimaculatus. By means of histological examination of an eye with fundus flavimaculatus they proved that the primary affection is located in the cells of the pigment epithelium.

The transmission of drusen of Bruch's membrane is autosomal dominant, usually in a regular manner (Pearce, 1967). General physical examination and routine laboratory tests generally show no abnormalities.

The differential diagnosis is between non-hereditary drusen and other hereditary dystrophies which display white flecks in the retina. Fundus flavimaculatus and fundus albipunctatus are such dystrophies and have a retinal function profile almost identical to dominant drusen. For this reason Krill and Klien (1965) grouped these conditions together under the title of "flecked retina syndrome".

In Stargardt's disease, which has to be differentiated from dominant drusen, many white flecks may be present at the posterior pole. This condition may be indistinguishable from fundus flavimaculatus when the latter is complicated by a foveal dystrophy. Retinitis punctata albescens and Bietti's tapeto-retinal dystrophy with marginal corneal dystrophy (Bagolini and Ioli-Spada, 1968) also present a white flecked retina.

Kandori's "fleck retina with congenital hemeralopia" might be yet another distinct entity, although Klien and Krill (1967) supposed that the cases described by Kandori, Setogawa, and Tamai (1965) might possibly fit into the fundus flavimaculatus category. This is doubtful, however, because congenital hemeralopia is not found in fundus flavimaculatus, and furthermore the flecks described by Kandori and others (1965) are much bigger than the small fishtail lesions found in fundus flavimaculatus (Kurimoto and Fukunaga, 1969). Capillarosis and "focal choroidopathy" (Yeates, 1960) show very tiny white flecks and are therefore easily differentiated.

Summary

In one family there were eight individuals with dominantly inherited drusen of Bruch's membrane, including a pair of identical twins and two boys aged 12 and 14 years.

In a second family the same condition was found in a mother and her daughter.

The interfamilial differences in the ophthalmoscopic appearances of this dystrophy are stressed. As Doyne's honeycomb dystrophy and malattia leventinese are indistinguishable entities and therefore probably due to the same gene, it is proposed to use the term "dominant drusen of Bruch's membrane" for this condition. Thus the complicated nomenclature of Tay's choroiditis, Holthouse-Batten's choroiditis, Doyne's honeycomb choroiditis, and malattia leventinese can be avoided.

It is assumed that this is a primary dystrophy of the cells of the retinal pigment epithelium.

Mr. A. L. Aan de Kerk took the photographs, Dr. A. Craandijk M.D. provided the fluorescein photograph, and Mrs. L. H. M. van Duyn prepared the manuscript.

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Leiomyoma of the ciliary body

A clinico-pathological case report

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Although partial cyclectomy has become an established procedure for the excision of tumours of the ciliary body, difficult clinical decisions are required before embarking on this surgery. Anxiety is caused especially by the uncertainty of unduly disturbing a large malignant lesion and by the surgical risks to the eye in relation to the chances of success in maintaining the integrity of the eye and possible vision. The larger the tumour the more the uncertainty, and hence the interest of this case.

Case report

A housewife aged 24 years was seen by Dr. Veronica Hughes at the Angau Memorial Hospital, Lae, New Guinea, on August 6, 1968. She had accidentally discovered that the visual acuity of the right eye was poor only 2 weeks previously. At that time it was 6/24, with +2 D cyl., 90°. In the left eye the unaided vision was 6/5. She was referred to Melbourne for treatment.

EXAMINATION (December 4, 1968: R.F.L.)

The right eye was free of inflammation and showed a large, almost smooth, brown tumour behind the iris in the 12 o'clock position, considerably indenting the equator of the lens and presumably arising from the ciliary body. Gonioscopy showed the peripheral iris bulging in two places at the 12 o'clock position thereby closing the angle but apparently by iris apposition and not by adhesions or infiltration. Elsewhere the angle was open. Transillumination was negative indicating the absence of a cyst.

When the pupil was dilated with cyclopentolate eyedrops the iris moved freely over the mass exposing more of it and the adjacent lens which was deeply indented and contained heavy local opacities (Fig. 1). The tumour appeared confined to the ciliary body with no extension into the retina. The ocular tension was normal.

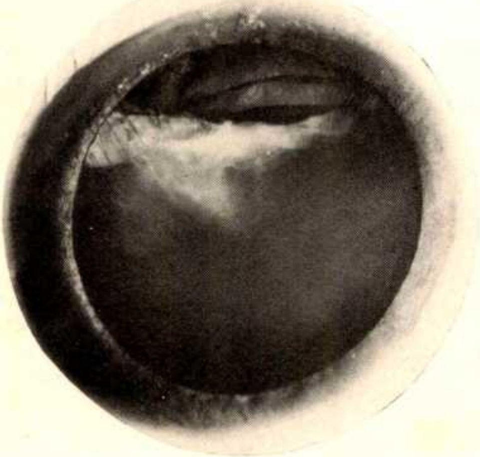

FIG. 1 *Large tumour of ciliary body indenting the lens and causing extensive local opacities*

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DIAGNOSIS

The patient was of the Phillipino race born in Manila. In view of her age and the localized appearance of the tumour, and because malignant tumours of the uveal tract are relatively rare in Asians, a clinical diagnosis of probably benign tumour of the ciliary body was made and removal by partial cyclectomy was recommended.

SURGERY

On December 18, 1968, after intensive administration of oral acetazolamide and intravenous mannitol, a partial cyclectomy was performed, using the method described by Stallard (1961) as a guide. At the 12 o'clock position a fornix-based conjunctival flap was reflected, a 180° limbal incision was cut with razor blade and scissors, and a Y-shaped incision was made extending back to the superior rectus tendon. Using a cyclodialysis spatula, flaps were mobilized and diathermy was applied to the edges of the ciliary body around the tumour.

The tumour could be vaguely identified and the iris was snipped across just anterior to the iris root. The tumour then presented and was held by an erisophake while it was lifted and the ciliary body incised around it, so that it could be totally removed. No vitreous was lost; the lens was not seen. The limbus incision was closed with virgin silk sutures, the sclera by white silk. The fornix-based flap was drawn down and sutured at the sides to cover the wound.

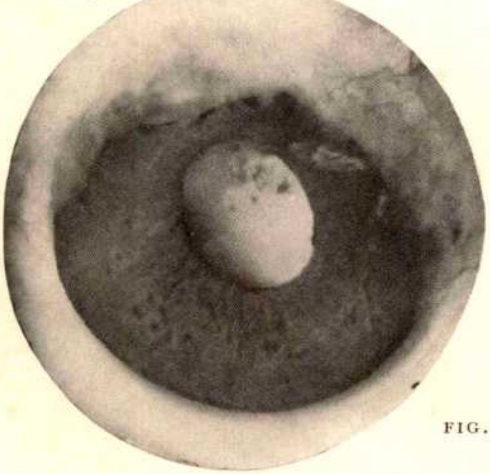
Postoperative progress was slow but uneventful. The anterior chamber reformed slowly but remained clear, and the pupil was roughly circular. Atropine eyedrops were used to assist in tightening the zonule to minimize anterior lens displacement, but atropine sensitivity required their cessation after several weeks.

The patient returned to New Guinea under the supervision of Dr. Veronica Hughes. One month after operation the corrected visual acuity was still 6/24 although lens clouding had increased. The optic disc and retina could be seen vaguely and appeared intact.

REVIEW AFTER 12 MONTHS

The patient was re-examined (by R.F.L.) in Melbourne in January, 1970. The right eye was free from inflammation and cosmetically good in alignment and appearance. The upper eyelid hid the operation scars.

Apart from these scars the cornea was clear. The right pupil was semidilated and roughly circular and many posterior synechiae were present with the upper iris plastered to the lens. The lens was translucent white and tilted forwards above with the upper lens equator adherent to the operation scar (Fig. 2). The right anterior chamber was 2·4 mm. deep at the centre, whereas the left anterior chamber was 2·8 mm. deep. Gonioscopy showed the angle widely open in the lower quarter in the right eye, but in the other three-quarters, the angle was smothered by iris at the sides and by lens above (Fig. 3). Applanation tonometry showed that the ocular tension was 17 mm. Hg in each eye.



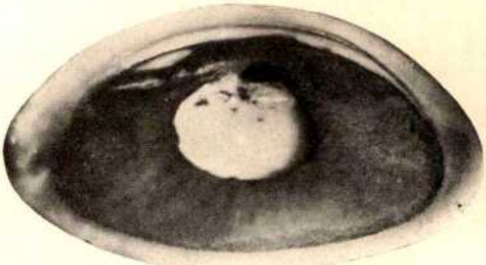


FIG. 3 *Postoperative goniophotograph, showing iris and lens adherent to partial cyclectomy scar*

FIG. 2 *Right eye one year after excision of ciliary body tumour*

The visual acuity in the right eye was reduced to perception of hand movements, but light projection was very quick and accurate in all areas. The eye appeared generally healthy and in good condition.

Lens removal by irrigation appeared possible, but this was deferred because the patient was returning to New Guinea where ophthalmological attention would not be available. Contact lens wearing seemed too difficult.

Pathology report (C.H.G.)

Macroscopic appearances The specimen was an ovoid tumour measuring 8 × 6 × 5 mm., with a smooth dark brown external surface and a yellowish-grey finely granular cut surface (Fig. 4).

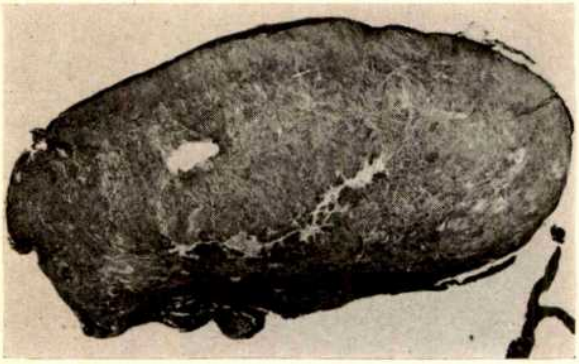


FIG. 4 *Section through the whole leiomyoma stained with phosphotungstic-acid haematoxylin* ×8

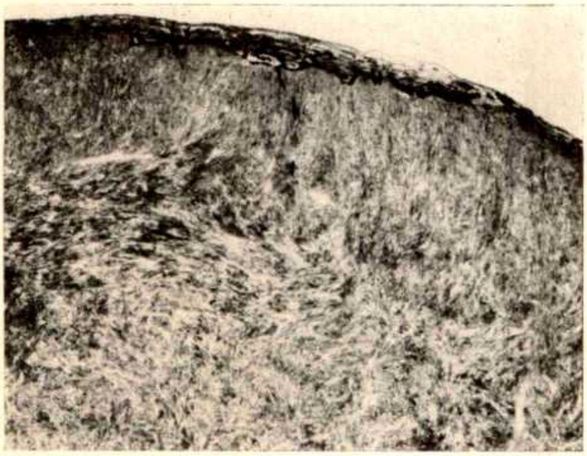


FIG. 5 *Section of leiomyoma, showing bundles of neoplastic spindle cells* ×50

Microscopic appearances Sections showed a typical leiomyoma of neoplastic spindle cells (Fig. 5) which fulfilled all the histological criteria cited below. The outer aspect of the growth was invested by the compressed tissues of the ciliary body in which many seams of pigmented ciliary epithelium were evident (Fig. 6). Part of the iris was attached to one pole. The tumour was rich in myofibrils (Fig. 7). Scanty reticulin fibres and small numbers of uveal melanocytes were dispersed among the tumour cells. In the base of the growth, where it had been attached to the ciliary body, normal ciliary muscle was recognizable, the orderly arrangement of its cells contrasting with the more haphazard disposition of those constituting the tumour.

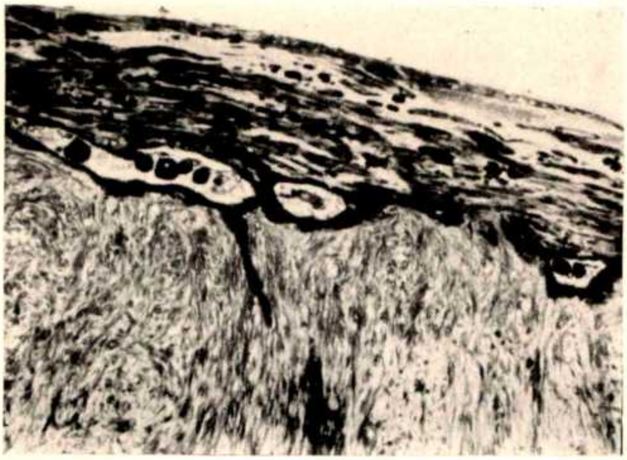


FIG. 6 *Section of leiomyoma, showing pseudocapsule of compressed ciliary epithelium* ×225

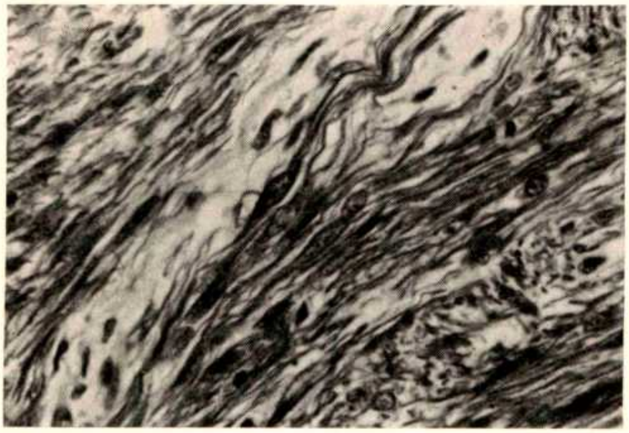


FIG. 7 *Typical field of tumour cells stained with phosphotungstic-acid haematoxylin to show myofibrils* ×900

Discussion

Leiomyomata of the ciliary body are very rare tumours. A review of the world literature (Blodi, 1950) revealed only ten reported cases, none of which was entirely acceptable by modern histological criteria. These criteria comprise the following features:

(1) The tumour is composed of interlacing compact bundles of spindle-shaped cells which may exhibit palisading. There is very little intervening collagenous stroma.

(2) The tumour cells contain oval nuclei with rounded ends.

(3) The tumour cells have eosinophilic fibrillary cytoplasm due to the presence of longitudinally orientated intracellular myofibrils which stain purplish blue with phosphotungstic-acid haemotoxylin.

Blodi (1950) presented a description of the first ciliary body leiomyoma to fulfil the above criteria. Ten additional authentic cases have since been reported, seven of which came from the files of the Armed Forces Institute of Pathology (Meyer, Fine, Font, and Zimmerman, 1968).

Summary

A large ciliary body mass diagnosed as a benign tumour was removed by partial cyclectomy. Clinically the dark brown tumour was presumed to be composed of pigment cells, but the dark colour was derived merely from ciliary epithelium stretched over a cream leiomyoma. Increased lens opacities prevented useful vision but the eye remained cosmetically good and generally healthy. The prospects of improving the vision by cataract removal and the wearing of a contact lens were deferred but not abandoned.

The clinical photographers of the Hospital (Mr. T. F. Cottier and Mrs. P. Silberman) gave considerable help.

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The heart in Leber's optic atrophy

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Patients with Leber's optic atrophy may have diffuse neurological disease with involvement of systems other than the nervous system (Ferguson and Critchley, 1928; Wilson, 1963; Bruyn and Went, 1964; Adams, Blackwood, and Wilson, 1966). These findings suggest that Leber's disease, although mainly affecting the optic nerves, is a multisystem disorder. Cardiac abnormalities have not been described in Leber's disease apart from an account of myocardial disease found *post mortem* in one patient (Wilson, 1963). This paper reports the electrocardiographic changes found in two patients with Leber's disease.

Case reports

Case 1, a capstan operator, was admitted to hospital in June, 1967, at the age of 24 years.

History

He had good vision until November, 1963, when he developed progressive painless blurring of central vision in the right eye over a period of 4 to 5 weeks, and 2 months later the vision in the left eye became similarly affected. He was admitted to hospital where he was found to have oedematous optic discs and dense central scotomata. The visual acuity in the right eye was counting fingers, and in the left eye 6/60.

Physical examination at that time showed no abnormality and investigations including *x*-rays, lumbar puncture, and air encephalography gave normal results. Since then the vision had remained poor in both eyes. He had no history of cardiorespiratory symptoms or other past illness. He had never smoked. Two maternal uncles had optic atrophy, with a similar history of rapidly progressive bilateral visual loss; one of them showed marked subsequent improvement. A male child of one of the affected uncles was born with a clubfoot deformity.

Examination

In June 1967, there was bilateral optic atrophy with dense central scotomata; the visual acuity in both eyes was hand movements at 1 m. The blood pressure was 120/80 mm. Hg, and the electrocardiograph was abnormal (Fig. 1; Table I), but further investigations, including chest *x*-ray and radiological screening of the heart, gave normal results. The electrocardiograph of the patient's father was normal; no other members of the family were available.

Case 2, a postgraduate research worker, was admitted to hospital in March, 1967, at the age of 28 years.

History

His vision had been good until December, 1961, when he developed simultaneous painless rapidly progressive blurring of the central vision in both eyes, while studying in Israel. He was admitted to hospital where he was found to have oedematous optic discs and central scotomata; the visual acuity in the right eye was counting fingers at 0·5 m., and in the left 3/60. Skull *x*-rays and lumbar puncture were normal, but air encephalography showed a doubtful abnormality in the chiasmatic

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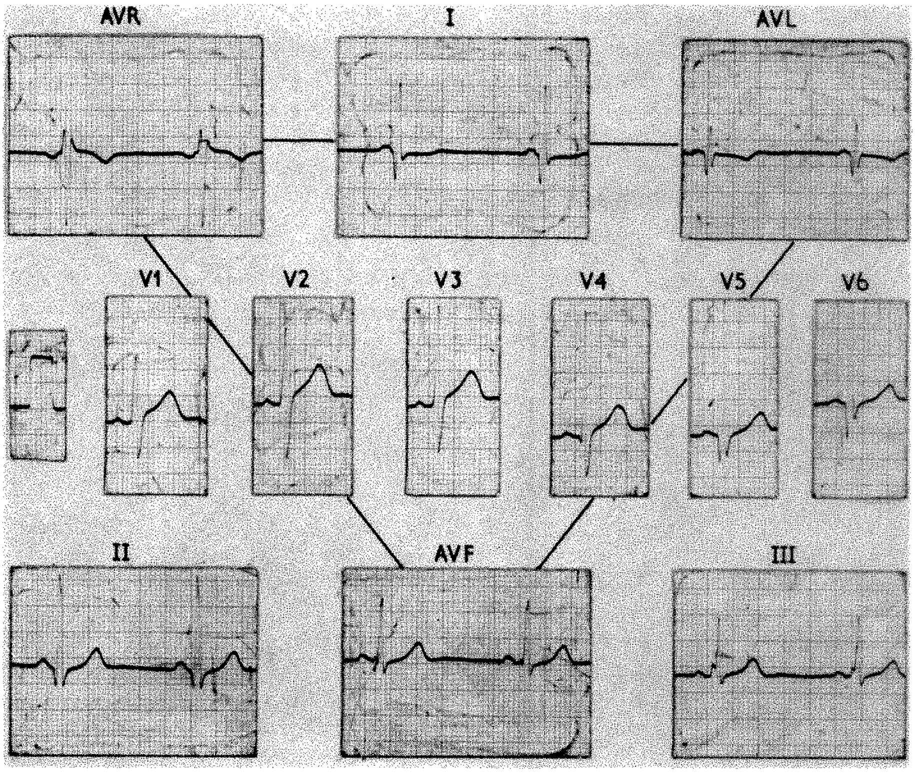

FIG. 1 *Electrocardiograph of Case 1*

Table I *Electrocardiographic findings in Cases* 1 *and* 2

Case no.	1	2
Rhythm	Sinus	Sinus
Rate/min.	60	60
P wave	Normal	Normal
PR interval (sec.)	0·12	0·16
Q wave	Prominent in I, II, AVL, $V_{5,6}$	Prominent in II, III, AVF, V_{4-7}
R wave	>25 mm. in V_{4-6}	>25 mm. in II, III, AVF, V_{5-7}
	$RV_1 > SV_1$	Tall in V_1
$SV_1 + RV_5$ (mm.)	45	41
QRS (sec.)	0·10	0·08
ST	Elevated V_{1-4}	Elevated $V_{2,3}$
T wave	Low voltage in I	Normal
QT_c (sec.)	0·40	0·40
Frontal plane axis	+55°	+70°

cistern. The vision failed to improve with ACTH injections. Craniotomy in February, 1962, was negative, the appearance of the optic nerves and chiasm being normal. In the 6 months after the operation the vision improved but had not changed since. In 1955, while in South Africa, the patient had had an episode of unconsciousness and had been kept in bed in hospital for 3 weeks. An electrocardiograph performed at that time was abnormal. He had no other cardiorespiratory symptoms or past illness. He had smoked fifteen cigarettes daily for 10 years. There was no known family history of eye or neurological disease; a brother, sister, and two maternal uncles were well.

Examination

In March, 1967, he was normal apart from bilateral optic atrophy and central scotomata; the visual acuity was 2/60 in both eyes. The blood pressure was 130/75 mm. Hg, and the electrocardiograph was abnormal (Fig. 2; Table I). Further investigations, including chest *x*-ray, gave normal results. The electrocardiograph taken in South Africa in 1955 was obtained and this was identical with the 1967 recording. No members of the family were available for examination.

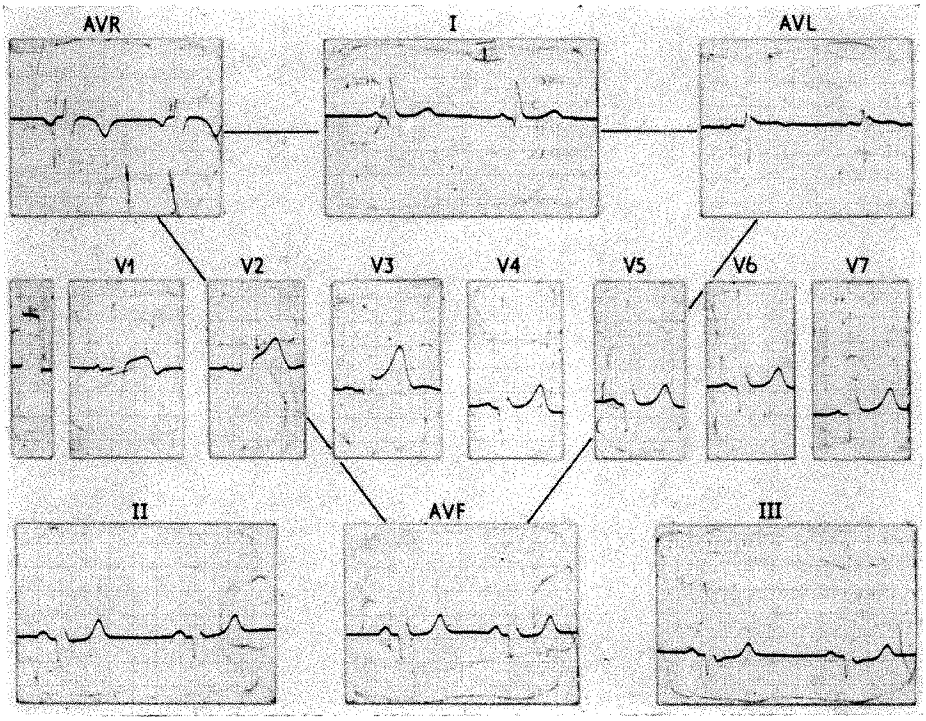

FIG. 2 *Electrocardiograph of Case 2*

Electrocardiographs were obtained in four further unrelated male patients with Leber's hereditary optic atrophy and these were all normal.

Discussion

Leber's disease usually affects males in early adult life, who typically suddenly develop bilateral loss of central vision. Subsequently, vision may improve as optic atrophy develops. The family history is characteristic with unaffected females transmitting the condition to males who are affected but do not transmit. The exact mode of inheritance is not known (Rose and Friedmann, 1964; François, 1966). Of the present patients, Case 1 has the classical features and family history of Leber's disease. The features in Case 2 are also typical but the family history is negative, though this is by no means excludes the diagnosis (Lundsgaard, 1944; Hierons and Lyle, 1959).

Although there have been several reports of cardiac involvement in heredofamilial neurological disorders, there has been only one in which the heart was involved in Leber's disease. This was a patient with Leber's disease and progressive dementia who had complained of breathlessness on exertion, chest pain, and palpitations for a few years before his sudden death at the age of 41 years. *Post mortem* examination revealed a dilated heart with abnormal myocardium and only slight coronary atheroma, and these features were thought to be consistent with cardiomyopathy (Wilson, 1963).

Syncopal attacks have been described in patients with Leber's disease in the absence of other evidence of heart disease, but electrocardiography was not performed in these patients (Ferguson and Critchley, 1928; Wilson, 1963).

The electrocardiographic abnormalities found in the two patients reported are very similar and occur in the absence of clinical or radiological evidence of cardiovascular disease. The main abnormalities are deep Q waves and tall R waves in limb and chest leads (Table I). Deep Q waves may be found in the normal in association with, and less than 25 per cent. of the height of, tall R waves, and less than 0·04 sec. duration; tall R waves are not in themselves abnormal, especially in the young (Goldman, 1964). Abnormally deep Q waves are found in myocardial infarction and ventricular hypertrophy, but there is no other evidence to support such diagnosis in these two patients. Abnormal Q waves are also found in association with hypertrophy of the interventricular septum in muscular subaortic stenosis (Braudo, Wigle, and Keith, 1964), when septal muscle is spared in the cardiomyopathy of progressive muscular dystrophy (Perloff, de Leon, and O'Doherty, 1966; Perloff, Roberts, de Leon, and O'Doherty, 1967), and in familial cardiomyopathy in which there is myofibrillar hypertrophy as well as patchy atrophy and fibrosis (Whitfield, 1961). It seems that the present patients might have a mild degenerative cardiomyopathy with sparing or hypertrophy of the interventricular septum and insufficient to produce clinical or radiological signs.

The heredofamilial neurological disorders which may have associated electrocardiographic abnormalities are summarized in Table II (overleaf). In those diseases in which bilateral optic atrophy occurs the cardiographic changes are unlike those in the present report, and are associated pathologically with disease of the myocardium, Purkinje fibres, or sinoauricular node.

Affected patients may have diffuse neurological disease with features of lower motor neurone, upper motor neurone, cerebellar, extrapyramidal, or cortical involvement (Ferguson and Critchley, 1928; Wilson, 1963; Lees, Macdonald, and Aldren Turner, 1964; Bruyn and Went, 1964; Adams and others, 1966). These associations suggest a link between Leber's disease and other heredofamilial neurological disorders in which optic atrophy occurs (Ferguson and Critchley, 1928; v Bogaert, 1948; Bruyn and Went, 1964). To explain the multisystem involvement in heredofamilial neurological disease it has been suggested that the abnormal gene is pleiotropic (Roth, 1948; Boyer, Chisholm, and McKusick, 1962; Rose, Fraser, Friedmann, and Kohner, 1966). Assuming a single gene abnormality in Leber's disease, the possibility that cardiac muscle may be involved provides evidence for pleiotropy of this gene. Since cardiac involvement occurs in other heredofamilial neurological diseases, the presence of electrocardiographic abnormalities in cases of Leber's disease lends some support to a relationship, however distant.

Table II *Heredofamilial neurological syndromes associated with electrocardiographic abı*

Syndrome	*Inheritance*	*Optic atrophy*	*Cardiographic abnormalities*	*Reference*
Friedreich's ataxia	Variable	+	Dysrhythmia T inversion	Boyer and other
Peroneal muscular atrophy	Variable	+	Dysrhythmia Flat T	Leak (1961)
Hereditary spastic paraplegia	Variable	+	Dysrhythmia Conduction defects	Sutherland (195
Refsum's disease	Recessive	—	Conduction defects T inversion	Gordon and Hu
Congenital nerve deafness	Recessive	—	Prolonged QT_c Large T	Fraser, Froggatt (1964)
Pseudo-hypertrophic muscular dystrophy	Sex-linked	—	Dysrhythmia Deep Q Tall RV_1	Perloff and othe Perloff and othe
Ocular myopathy	Variable	—	Conduction defects	Kearns and Say
Dystrophia myotonica	Variable	—	Dysrhythmia T inversion Conduction defects	Cannon (1962)

Summary

Electrocardiographic abnormalities are reported in two patients with Leber's l optic atrophy. Electrocardiographs in four further patients with Leber's dis normal. The significance of these findings in relation to possible cardiac path to the pathogenesis of Leber's disease is discussed.

We thank Dr. M. Harington, M.R.C.P., for advice on the interpretation of the electrocardio Mr. A. I. Friedmann, F.R C.S., for his help and co-operation.

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Prednisolone-21-stearoylglycolate in scleritis

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Scleritis is one of the collagen diseases. It is a serious condition often accompanied by severe pain and the disabling ocular complications of keratitis, uveitis, glaucoma, macular oedema, complicated cataract, retinal detachment, and even perforation of the globe. In its characteristic form the disease is recurrent, eventually becoming quiescent. Adequate treatment should be given at an early stage, aimed at suppression of the condition until natural remission occurs; otherwise there may be marked reduction in vision and loss of the eye.

In the Scleritis Clinic of the Professorial Unit at Moorfields Eye Hospital, the effects of oxyphenbutazone (Tanderil), Indomethacin, and systemic and local prednisolone have been compared. The present study is concerned with the effect of prednisolone-21-stearoylglycolate (Sintisone).

No satisfactory classification of scleritis exists in the literature. We have recently classified it as follows (Watson, Hayreh, Awdry, 1968a, c):

(1) Anterior scleritis

- (*i*) Nodular scleritis
- (*ii*) Diffuse scleritis
- (*iii*) Necrotizing scleritis, which includes scleromalacia perforans.

(2) Posterior scleritis

Further subdivision of this classification is not justified, as it is not related to the aetiology.

Materials

The study was carried out on 27 patients with lesions shown in Table I. Their ages ranged from 16 to 84 years (Table II), and there were thirteen women and fourteen men. Thirteen had some associated systemic disease or precipitating factor (Table III).

All but two of these patients had been treated with other drugs (Table IV), but these were discontinued during the trial. In mild cases of scleritis, local steroids were used. If the condition did not respond or was very severe, systemic anti-inflammatory drugs were given: Tanderil, Indomethacin, or prednisolone. Sintisone was given to 25 patients in whom there was no improvement, or a recurrence. Out-patients were assessed at weekly intervals.

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Table I *Nature of lesions*

Type of Lesion	*No. of cases*
Nodular scleritis	7*
Anterior diffuse scleritis	5
Sclero-keratitis	11**
Necrotizing scleritis	1
Posterior scleritis with retinal detachment	1
Diffuse anterior and posterior scleritis with uveitis and macular oedema	1
Bilateral diffuse episcleritis	1***
Total	27

* = One had episcleritis in the other eye
** = One had a marked uveitis
*** = This patient's condition did not respond to local steroids or to any systemic anti-inflammatory drugs other than steroids

Table II *Age distribution*

Age (yrs)	*No. of cases*
10–19	2
20–29	1
30–39	1
40–49	10
50–59	7
60–69	3
70–79	2
80–89	1
Total	27

Table III *Cases with associated systemic disease*

Systemic disease	*No. of cases*
Rheumatoid arthritis	5
Osteoarthritis	2*
Herpes zoster ophthalmicus	2
Enteritis (most probably ulcerative colitis)	1
Sensitivity to industrial solvents	1
Raised ESR with no other systemic abnormality	1
Xanthomatosis	1
Total	13

* = In one of these there was a persistently raised ESR

Table IV *Treatment given before Sintisone trial*

Treatment	*No. of cases*
Local steroids	12
Local steroids and Tanderil	2
Local steroids and Indomethacin	1
Local steroids and systemic prednisolone	2
Local steroids, Tanderil, and Indomethacin	1
Local steroids, Tanderil, Indomethacin, and systemic prednisolone	4
Local steroids, Tanderil, Indomethacin, systemic prednisolone, and ACTH	3
No treatment	2
Total	27

Dosage

One tablet of prednisolone-21-stearoylglycolate contains 6·65 mg. and is equivalent to prednisolone 3·5 mg. The period of maximum dosage (Table V, overleaf) depended upon the response of the lesion: this dose was continued for 7 to 14 days, in three cases for 21 days, and in one for 28 days (these four patients received eight tablets per day). Once the response was satisfactory, as judged by the disappearance of pain and inflammation, the dose was reduced gradually. In most patients the reduction in dosage was to 6, 4, 3, 2, and 1 tablet a day, at intervals of about 4 to 7 days. The drug was then withdrawn. In patients in whom the disease tended to recur on the above regime of reduction of dosage, it was necessary to reduce the dose in half-tablet steps. There were some, however, who needed a maintenance dose and the drug could not be withdrawn completely.

Table V *Dosage of Sintisone during initial period*

No. of Sintisone tablets per day (expressed as prednisolone in mg.)	*No. of cases*
12* (42 mg.)	1
8 (28 mg.)	17
6 (21 mg.)	6
4 (14 mg.)	3
Total	27

*One tablet of Sintisone (6·65 mg.) is equivalent to prednisolone 3·5 mg.

Table VI *Complete resolution of scleritis with Sintisone*

Time of onset	*No. of cases*
2 days	1
4 days	7
5 days	3
6 days	1
1 wk	6
2 wks	1
4 wks	2
Total	21

Table VII *Incomplete resolution of scleritis with Sintisone*

Time of onset	*No. of cases*
2 days	1
4 days	1
2 wks	2
4 wks	1
Total	5

Results

The result was assessed as complete resolution of the lesion, incomplete resolution, or no response. The last was recorded in only one patient, who stopped taking the drug after one week because the symptoms were not relieved. 21 cases showed complete resolution of the scleritis (Table VI), and in five the condition improved but there was incomplete resolution over a period of 4 weeks (Table VII).

The incidence of recurrence of the scleritis in 26 patients of this series was recorded during a follow-up period which varied from one month to 2 years (Table VIII). In sixteen cases cessation or reduction of the dosage was followed by a recurrence of scleritis, and the initial regime had to be repeated. Thirteen patients required a maintenance dose to keep them free from recurrent attacks (Table IX).

Table VIII *Incidence of recurrence of scleritis*

Follow-up period (mths)	*Recurrence*	
	Absent	*Present*
1	–	1
2	1	1
3	2	–
4	–	1
6	–	1
8	1	1
12	1	1
13	1	–
14	1	–
16	1	1
18	1	3
24	1	6
Total no. of cases	10	16

Table IX *Maintenance dose of Sintisone*

Dose (tablets)	*No. of cases*
1 alternate days*	1
1 daily	2
1½ daily	1
2 daily	7
4 daily	2
Total	13

*Equivalent to prednisolone 3·5 mg.

In four patients Sintisone was withdrawn, for the following reasons:

(1) Acute psychosis with suicidal tendencies developed in two women aged 52 and 54 years. In the first, the psychosis started towards the end of the first week of treatment with eight tablets per day,

and became severe during the second week (six tablets per day). The drug was tailed off to a complete stop in 48 hours and recovery was dramatic. The scleritis in the meantime had resolved completely. In the second patient, the psychosis developed 4 weeks after treatment with eight tablets per day and there was complete recovery when the drug was discontinued. This patient showed no evidence of psychosis on prolonged treatment with prednisolone before and after the Sintisone. The scleritis had resolved partially with Sintisone, but was completely suppressed by prednisolone.

(2) In one patient showing sensitivity to industrial solvents there was no response to Sintisone during the first week. He stopped taking it and asked to return to prednisolone, of which he now requires a maintenance dose of 40 mg. which just controls the scleritis.

(3) In one woman aged 84 with scleromalacia perforans, Sintisone achieved only incomplete resolution of scleritis over a 4-week period and the lesion flared up when the dose was reduced to less than six tablets daily. Suppression was achieved with prednisolone 80 mg. daily.

The associated systemic conditions (Table III) also improved whilst the patients were receiving Sintisone. In one patient, enteritis of long duration, probably ulcerative colitis, responded very satisfactorily, and this patient is symptom-free on a maintenance dose of two tablets daily. All the patients with rheumatoid arthritis noticed an improvement.

Side-effects

Noticeable side-effects were recorded in only three patients. As mentioned above, acute psychosis with suicidal tendencies was seen in two. One patient, a woman of 57, complained of hot flushes on the initial dosage. No significant gastrointestinal symptoms were reported. In one patient, who had a tendency to "indigestion", this was slightly more marked. In another, however, with a history of gastric ulceration, there were no symptoms on a maintenance dose of two tablets per day for 8 months; and during two further periods of treatment with larger doses because of recurrence of scleritis, there has been no clinical or *x*-ray evidence of gastric ulceration.

There was no significant gain in weight in these patients. In fact, some who had gained in weight on treatment with prednisolone commented that they lost weight on changing to Sintisone.

No other side-effect was noticed in this series, though no detailed systemic examination was carried out and reliance was placed on the patients' own statements.

Discussion

All but two of the patients in this series had received treatment for scleritis before they were given Sintisone (Table IV). In our experience of the response of scleritis to different drugs (Watson, Lobascher, Sabiston, Lewis-Faning, Fowler, and Jones, 1966; Watson and others, 1968b, c), we have found that local steroids are effective in only a minor proportion of the patients with mild scleritis, oxyphenbutazone 600 mg. per day in about 50 per cent., Indomethacin 100 mg. per day in about 50 per cent., and systemic prednisolone 60 to 120 mg. per day in 100 per cent. In the present series Sintisone was found to be as effective as prednisolone in all except the two mentioned above (Nos. 2 and 3). On comparing the dosage of Sintisone with that of prednisolone in scleritis, we have found that initially the effective dose is the equivalent of prednisolone 28 to 42 mg. as compared to prednisolone 60 to 120 mg. per day. The response of scleritis to Sintisone and prednisolone is, in the majority of cases, dramatic; but systemic steroids are suppressive and not curative, and when the drug is stopped the symptoms recur (Table IX). The rate of recurrence with Sintisone as compared with prednisolone cannot be assessed accurately. Apart from the acute psychosis in two patients in this series, no significant side-effects, and none of those commonly associated with other systemic corticosteroid therapy (particularly fluid retention), were noticed. The absence of fluid retention and glaucoma with Sintisone was also reported by Sharma, Hayreh, and James (1968).

Thus it can be concluded that, in the treatment of scleritis, Sintisone is as effective as any other steroid and more effective than Tanderil or Indomethacin. It has fewer side-effects than prednisolone. The effective initial dose is usually eight tablets daily, reducing gradually as soon as a response has been obtained. Patients who require a high maintenance dose of prednisolone also require a high maintenance dosage of Sintisone but, in view of the very similar therapeutic response with a comparatively lower dose and fewer side-effects, it would seem reasonable that Sintisone should be used in preference to prednisolone.

Summary

A clinical trial of systemic Sintisone was carried out in 26 patients with scleritis and one with marked episcleritis. It was as effective in these cases as any other corticosteroid. The only major side-effect noticed was acute psychosis in two patients, which promptly disappeared on cessation of treatment. The initial effective dose was eight tablets daily, equivalent to prednisolone 28 mg., reducing gradually as soon as a clinical response was obtained.

We are grateful to Dr. A. C. Marus of Carlo Erba (U.K.) Ltd., for his help and co-operation and for the supply of Sintisone, and to Prof. B. R. Jones for providing facilities for the trial.

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Conjunctival and corneal changes in renal failure

Influence of renal transplantation

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Secondary calcareous degeneration of the conjunctiva or cornea may follow such pathological conditions of the eye as spring catarrh, erysipelas of the lids, leucomata, uveitis, trauma, etc. On the other hand, primary calcareous degeneration is rare (Duke-Elder and Leigh, 1965); the corneal deposits occur on Bowman's membrane and the superficial layers of the stroma, acting as foreign bodies and causing irritation.

In otherwise normal eyes, conjunctival and corneal calcium deposits may be found in conditions involving hypercalcaemia, especially hyperparathyroidism, sarcoidosis, and vitamin D intoxication. Reports from Walsh and Howard (1947) and Cogan, Albright, and Bartter (1948) describe lesions observed in hyperparathyroidism. Changes in cases of sarcoidosis have also been reported by Friedman (1951), Cogan and Henneman (1957), and by Crick, Hoyle, and Smellie (1961). Patients receiving large amounts of vitamin D and exhibiting calcium deposits were described by Frost, Sunderman, and Leopold (1947), Walsh and Howard (1947), Cogan and others (1948), Gifford and Maguire (1954), Leira (1954), Gartner and Rubner (1955), and Smith (1957); in most of these patients the vitamin D had been given for rheumatoid arthritis.

Roentgenologic examination of the anterior portion of the eyeball may reveal calcification (Fleischner and Shalek, 1949; Gartner and Rubner, 1955).

Cogan and others (1948) observed calcium deposits in eight patients with severe renal damage, five of them with a history of high calcium and high alkali intake. In two other cases there was prolonged vomiting with chronic alkalosis. All had high serum levels of non-protein nitrogen and phosphorus. The calcium level was high in all but one case.

Berlyne and Shaw (1967) reported fifteen patients with severe renal failure, either acute or chronic, high serum inorganic phosphate, normal or low serum calcium, mean serum calcium × phosphorus product greater than 70, red eyes, and calcium deposits in the conjunctiva and cornea. Further evidence of conjunctival calcification in renal failure was offered by Berlyne (1968).

The present paper reports the findings in a group of five patients with chronic renal failure in whom red eyes became gradually manifest.

Methods

A group of five patients in the terminal stages of renal failure who were seen at the University Hospital exhibited signs of conjunctival reddening and irritation. Serial determinations of serum levels of calcium, phosphorus, alkaline phosphatase, creatinine, and urea were carried out. Peritoneal dialyses were performed several times at various intervals.

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Only three patients received a kidney transplant. In two a kidney from a living donor was used, and in the third from a cadaver. In all three the kidney was placed in the right iliac fossa.

Only one patient was examined with the slit lamp before and after surgery. A piece of bulbar conjunctiva of the right eye was surgically removed and studied under the microscope before the transplantation of a cadaver kidney. This patient was followed up for 20 weeks and biomicroscopy was carried out from time to time.

Results

The clinical and biochemical findings of the five patients with conjunctival congestion are presented in Table I, with later observations on the same patients when no redness was noticed, either in the earlier phase of renal failure or after they had undergone repeated peritoneal dialysis, followed in some cases by kidney transplantation.

Table I *Clinical and laboratory findings in five patients with renal failure with and without conjunctival congestion.*

Conjunctival congestion	*Case no.*	*Age (yrs)*	*Sex*	*Diagnosis*	*Serum calcium (mg./100 ml.)*	*Serum inorganic phosphorus (mg./100 ml.)*	*Serum Ca × P*	*Serum alkaline phosphatase (KA units/100 ml.)*	*Serum creatinine (mg./100 ml.)*	*Blood urea (mg./100 ml.)*	*Comment*
Present	1	34	F	P	7·2	13·4	96·48	10·9	26·0	300	
	2	25	M	G	8·1	16 9	136·89	4·0	28·0	288	
	3	27	M	G	8 8	17 0	149 60	3·6	25 0	330	
	4	28	F	G	7 8	16·5	128·70	2·2	20·0	206	
	5	35	M	G	7 6	16·3	123·88	7·4	22·0	243	
	Mean	29			7·9	16·0	126·40	5·6	24·2	273·4	
Absent	1	34	F	P	9·2	4·7	43 24	—	—	98	After repeated dialyses
	2	25	M	G	9 6	7·7	73 92	4·0	24·0	234	In steady state of renal failure
	3	27	M	G	8·5	2·7	22·95	—	1·2	50	After renal transplantation
	4	28	F	G	7·2	14·7	105·84	5·3	7·5	80	After repeated dialyses Aluminium hydroxide by mouth
	5	35	M	G	8·8	2 6	22 88	2·1	1·55	60	After renal transplantation
	Mean	29			8·6	6·4	55·04	3·8	8·56	104	

P = Chronic pyelonephritis G = Chronic glomerulonephritis

For the sake of comparison, the clinical and laboratory findings in eleven patients (Cases 6 to 16) with chronic renal failure but no redness of the eyes are presented in Table II (opposite).

Case 4 was examined with the slit lamp and had a piece of bulbar conjunctiva removed for microscopic examination.

Case report (Table I, Case 4)

A married woman aged 28 was admitted on March 5, 1968, with a history of cloudy urine for the last 10 years. During her first pregnancy, 5 years before, oedema, high blood pressure, dysuria, frequency of micturition, and proteinuria were noticed. The oedema persisted after the delivery of a premature stillborn infant. Three subsequent pregnancies followed the same pattern. Nausea, vomiting, paleness, and headaches were recorded for the last 3 months before admission. She was

Table II *Clinical and laboratory findings in eleven patients with renal failure and no conjunctival congestion.*

Case no.	*Age (yrs)*	*Sex*	*Diagnosis*	*Serum calcium (mg./100 ml.)*	*Serum inorganic phosphorus (mg./100 ml.)*	*Serum Ca × P*	*Serum alkaline phosphatase (KA units/100 ml.)*	*Serum creatinine mg./100 ml.)*	*Blood urea (mg./100 ml.)*
6	41	M	G	7·1	7·0	49·70	—	16·0	201
7	31	M	G	8·1	5·9	47·79	3·9	9·0	225
8	22	F	G	5·4	4·1	22·14	6·6	—	190
9	26	M	G	7·9	9·1	71·89	—	14·0	237
10	15	F	P	6·4	12·2	78·08	3·6	16·0	172
11	31	M	G	7·3	12·9	94·17	—	—	404
12	23	M	P	6·9	9·0	72·10	4·1	25·5	294
13	42	F	P	9·5	10·3	97·85	10·7	13·0	256
14	36	M	G	8·1	15·0	121·50	6·2	15·0	394
15	36	M	G	8·2	10·1	82·82	5·8	16·0	270
16	27	F	G	4·9	10·0	49·00	6·8	16·0	240
Mean	30	—	—	7·2	9·6	69·12	5·9	15·6	263

G = Chronic glomerulonephritis P = Chronic pyelonephritis

admitted with cardiac tamponnade caused by haemopericardium; this was successfully treated by surgery. The blood urea was 440/mg./100 ml. Peritoneal dialysis was performed at intervals of approximately 20 days and she was put on a low protein diet.

She complained of soreness of the eyes, which were congested. She was given aluminium hydroxide by mouth and peritoneal dialysis carried out at 10-day intervals. The eye symptoms improved temporarily (Table I) but later reappeared.

Examination

On April 16, 1968 a slit-lamp examination showed nasal and temporal pingueculae in both eyes and hyperaemia on the bulbar conjunctiva extending to the canthi. In the interpalpebral area both conjunctival and corneal changes were noticed. In the bulbar conjunctiva, both temporal and nasal, and above and below the pingueculae, delicate chalk-white structures were seen. They were either punctate or striate, appearing as peaks of light superficial to the vessels. The cornea showed hazy greyish superficial deposits running concentrically with the limbus, on both sides of the interpalpebral area. This zone was separated from the limbus by a narrow, less dense zone and faded off gradually toward the centre of the cornea (Fig. 1).

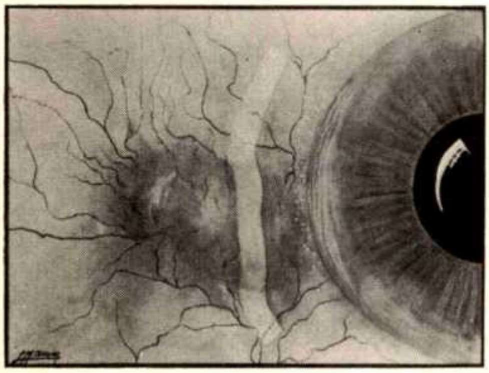

FIG. 1 *Photograph of slit-lamp painting of temporal aspect of right eye, showing pinguecula and calcium deposits in conjunctiva and cornea*

Biopsy

On April 18 a piece of bulbar conjunctiva was surgically removed from the right eye, immediately above the temporal pinguecula and adjacent to the limbus. The temporal pinguecula was removed separately. The material was preserved in 10 per cent. formalin, imbedded in paraffin, sectioned, and stained with haematoxylin and eosin.

Microscopical examination showed irregular thickness of the epithelium differentiated from the substantia propria. Many vessels, some of them dilated, and zones of basophilic degeneration were seen. Between the epithelium and the substantia propria there was a ribbon-like deposit of calcium salts. In the deeper layers of the substantia propria there were minute calcium deposits (Figs 2 and 3).

The pinguecula specimen showed no particular characteristics.

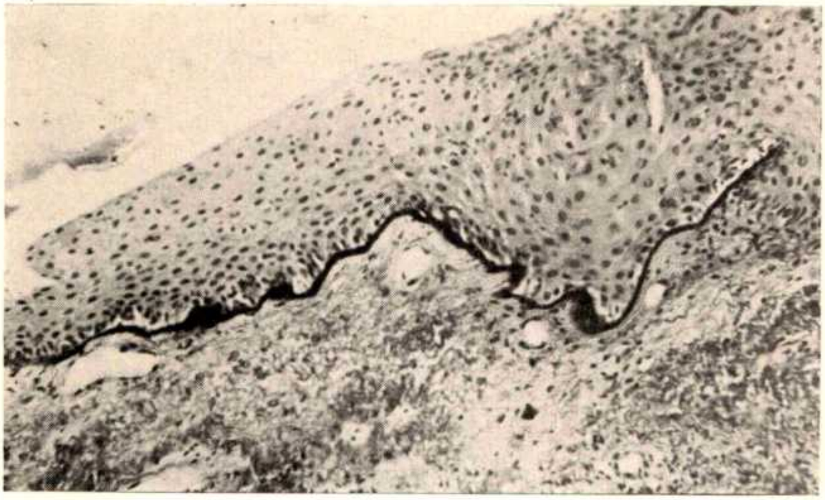

FIG. 2 *Conjunctival biopsy specimen, showing ribbon-like deposition of calcium between epithelium and substantia propria. Haematoxylin and eosin.* ×60

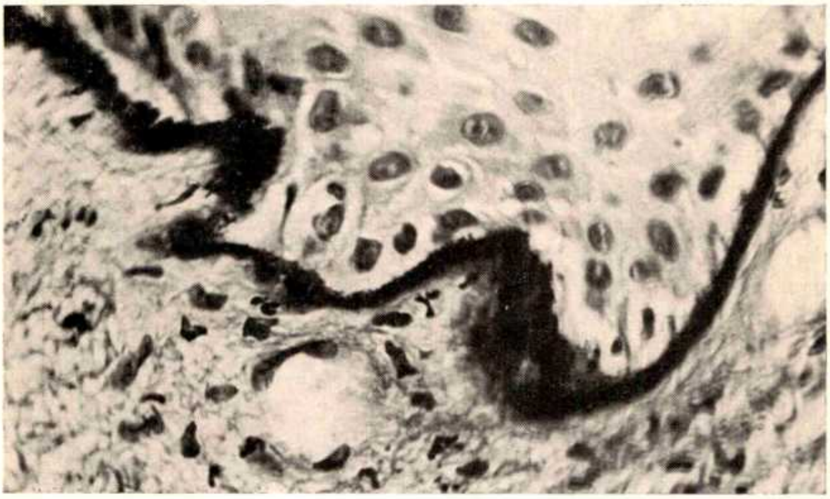

FIG. 3 *Higher magnification of part of Fig. 2.* ×240

Operation

On May 26 a cadaver kidney was transplanted.

Ocular progress

A slit-lamp examination was afterwards performed at regular intervals. At the first examination on June 6, both eyes showed a few conjunctival deposits temporally but none nasally; corneal deposits were seen both nasally and temporally but were inconspicuous.

On June 26 the right eye was unchanged but the conjunctival deposits in the left had disappeared and the corneal deposits had diminished.

On July 10 the conjunctival deposits in the right eye had diminished temporally and disappeared nasally; in the cornea they were unchanged temporally and less conspicuous nasally. In the left eye the pathological appearance of the cornea was less marked nasally and unchanged temporally.

On August 14 the aspect of both eyes was the same.

On September 13 the bulbar conjunctiva of the right eye was unchanged temporally but two deposits had reappeared nasally; the cornea was normal temporally and unchanged nasally. The left eye was normal, except for a slight loss of transparency of Descemet's membrane temporally.

On October 3rd the bulbar conjunctiva of the right eye was normal temporally but the two nasal deposits were still seen; the superficial cornea was unchanged but a small opacity in Descemet's membrane was seen inferiorly. In the left eye only one conjunctival deposit was observed temporally; in the cornea there was one deposit nasally and one temporally.

Termination

The patient died on October 12 from gastrointestinal haemorrhage. The postoperative course had been complicated by diabetes, infection with *E. coli*, and rejection of the transplant. The patient succumbed after nearly 5 months' heroic treatment.

Discussion

Red eyes in normocalcaemic or hypocalcaemic patients with renal failure, described by Berlyne and Shaw (1967), were considered to be early manifestations of small deposits of calcium in the vicinity of the limbus.

Berlyne (1968) found superficial conjunctival deposition of calcium in almost every patient with advanced renal failure who had a high calcium × phosphorus product (above 70) caused by a high plasma-inorganic-phosphate-level. These calcium deposits may be regarded as diagnostic.

The predilection for calcium deposition in the interpalpebral portion of the cornea and conjunctiva would be explained by loss of carbon dioxide to the atmosphere during the waking hours, with a fall in the pCO_2 of the superficial ocular tissues and consequent rise in the pH. The low pH of the plasma exhibiting a high calcium × phosphorus product, and a higher pH of both the aqueous humour and the superficial tissues would create favourable conditions for the deposition of calcium-phosphate salts.

Berlyne and Shaw (1967) suggested that the redness was a reaction to this deposition, the crystals being of such a size as to cause the inflammatory reaction.

The conjunctival lesions consist of reddening and calcification plaques. In the cornea an arc-shaped deposit of a whitish material concentric with the limbus is the outstanding finding. The presence of red eyes in the absence of infection or uveal inflammation should alert the physician to the possibility of renal failure. A slit-lamp examination will elucidate the picture.

In our patient the initial ocular findings were typical. After renal transplantation increased diuresis and lowering of the blood urea were observed. When the first postoperative slit-lamp examination was performed, 11 days after transplantation, the conjunctival deposits in both eyes had disappeared nasally and were greatly reduced temporally. The corneal deposits were still present but much reduced.

During subsequent weeks the eyes gradually cleared although two crises of rejection were detected and fought. The corneal deposits regressed more slowly than the conjunctival deposits.

When signs of renal failure occurred again a few conjunctival deposits reappeared and remained until the patient's death. A slight loss of transparency of Descemet's membrane at the periphery was observed in both eyes.

The information gathered from this single case suggests that the conjunctival and corneal deposits in renal failure are reversible, tending to disappear when the renal function improves.

Summary

The conjunctival and corneal changes in renal failure are described. One patient who received a kidney transplant was examined with the slit lamp at regular intervals. The conjunctival and corneal deposits tended to disappear, the first more readily than the second. A few conjunctival deposits reappeared when the renal function deteriorated.

We should like to thank Dr. Affonso Krug Filho for the microscopical report on the conjunctival specimen. We are indebted to Mrs. Lúcia Oliveira for the drawing (Fig. 1).

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Macular lesions during systemic therapy with depot tetracosactrin

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Ocular complications associated with long-term systemic corticosteroid therapy include the development of posterior subcapsular cataracts (Black, Oglesby, von Sallmann, and Bunim; 1960; Giles, Mason, Duff, and McLean, 1962; Crews, 1963; Spencer and Andelman, 1965; Fürst, Smiley, and Ansell, 1966; Williamson, Paterson, McGavin, Jasani, Boyle, and Doig, 1969), glaucoma (Alfano, 1963; Becker and Shaffer, 1965; Diotallevi and Bocci, 1965; Williamson and others, 1969), and scleral softening (Crews, 1965). In addition adrenocorticotrophic hormone has been implicated in the causation of posterior subcapsular cataracts (Crews, 1963), glaucoma (Alfano and Platt, 1966), and the simultaneous appearance of macular lesions and posterior subcapsular cataracts (Williamson and Dalakos, 1967).

This paper is concerned with the sudden development of bilateral macular exudates in a middle-aged man suffering from rheumatoid arthritis who was receiving large doses of depot tetracosactrin (Depot Synacthen, CIBA).

Case Report

A 45-year-old joiner was admitted to hospital with an 18-month history of sero-positive rheumatoid arthritis. He was incapacitated by active disease in many joints, despite treatment with salicylates, phenylbutazone, and indomethacin; latterly hospitalization and prednisolone (2·5 mg. three times a day) had failed to induce a remission of the disease or to control the symptoms.

There were no ocular symptoms and an ophthalmological examination gave normal results immediately before treatment with depot tetracosactrin was begun. This form of therapy had been started as intramuscular injections 0·5 mg. every 48 hours after the withdrawal of steroids in September, 1968. An immediate improvement in symptoms was accompanied by a gradual fall in the erythrocyte sedimentation rate and a rise in haemoglobin, and he was discharged from hospital 2 weeks after starting treatment with depot tetracosactrin. Owing to a misunderstanding, however, out-patient treatment was continued with alternate day injections of 1 mg., a much larger dose than that recommended for long-term therapy.

In December, 1968, he began to notice defective vision, particularly affecting the left eye. At this time he was noticeably Cushingoid and pigmented and had gained 8 kg. in weight. There was, however, no peripheral oedema; he remained normotensive and the rheumatoid arthritis remained in remission. The dose of depot tetracosactrin was then gradually reduced until in May, 1969, he was receiving 0·25 mg. every 72 hours and his visual acuity improved concurrently.

Laboratory investigations

Tests before starting treatment with depot tetracosactrin gave the following results: Hb 9·9 g./100 ml.; mean corpuscular haemoglobin concentration 34 per cent.; erythrocyte sedimentation rate

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(Westergren) 103 mm./hr; serum proteins 7·4 g./100 ml. (albumin 3·4; globulin 4·0); serum electrolytes, calcium, inorganic phosphorus, alkaline phosphatase, urea, and uric acid, all normal.

A joint *x*-ray survey showed erosive changes in many joints, whilst *x*-rays of the chest and sinuses were clear.

The Hyland RA latex-fixation test was strongly positive and the sheep cell agglutination test was positive in a titre of 1/64. An immunofluorescent test for antinuclear antibody was weakly positive (titre 1/16) and showed homogeneous staining (Beck, Anderson, McElhinney, and Rowell, 1962), but the L.E. latex test was negative, as were precipitin tests for thyroglobulin and immunofluorescent tests for antibodies to thyroid microsomes and gastric parietal cells.

Tests of hypothalamo-pituitary-adrenal function (plasma 11-hydroxycorticosteroid responses to tetracosactrin and insulin-induced hypoglycaemia (normal before treatment was begun).

A transient fall in serum potassium to 2·9 mEq/l. occurred and this was corrected by administration of potassium chloride (Slow-K-CIBA, 1·2 g. three times a day). When the ocular symptoms were evident, the serum electrolytes were normal, the haemoglobin had risen to 12·9 g./100 ml. and the erythrocyte sedimentation rate had fallen to 9 mm./hr. Intermittent glycosuria, with a blood sugar of 136 mg./100 ml. 2 hours after lunch, was noted at this time.

Ocular examinations

10 SEPTEMBER, 1968

Routine full ophthalmological examination revealed no abnormalities and no family history of ocular disease was obtained. The visual acuity was 6/6 and N5 in both eyes.

1 JANUARY, 1969

The patient gave a 4-weeks' history of defective vision, particularly affecting the left eye. There was no history of inflammation, pain, or haloes. Pupil reactions were normal. The visual acuity was 6/9 and N5 in the right eye and 1/60 and N24 in the left. Ophthalmoscopic examination of the right eye revealed small non-confluent exudates and a few superficial haemorrhages in the perifoveal region. The left eye, however, had developed a large raised plaque of oedema, of three disc diameters, covering the entire macular area. There were no large haemorrhages and the retinal vessels appeared normal (Fig. 1).

The right visual field charted on a Bjerrum screen showed a small relative central scotoma to 5/1000 red targets. The left visual field demonstrated a dense complete central scotoma to all targets extending to the 15° isopter and a partial scotoma to the 20° isopter to white targets (2/1000 and 5/1000) and to red targets (5/1000) and 10/1000). There was no evidence of glaucoma.

1 JUNE, 1969

The patient's ocular symptoms, which had begun to improve immediately the dose of depot tetracosactrin was reduced, had disappeared and a full ophthalmological examination gave normal results apart from some residual pigment in the left macular area (Fig. 2). The visual acuity was 6/6 and N5 in the right eye and 6/9 and N5 in the left.

JANUARY 1970

No further deterioration had occurred.

Discussion

Macular degeneration in association with posterior subcapsular cataracts has been reported during the course of therapy with natural corticotrophin (ACTH gel) (Williamson and Dalakos, 1967) and a central serous retinopathy was observed by Jain and Singh (1966)

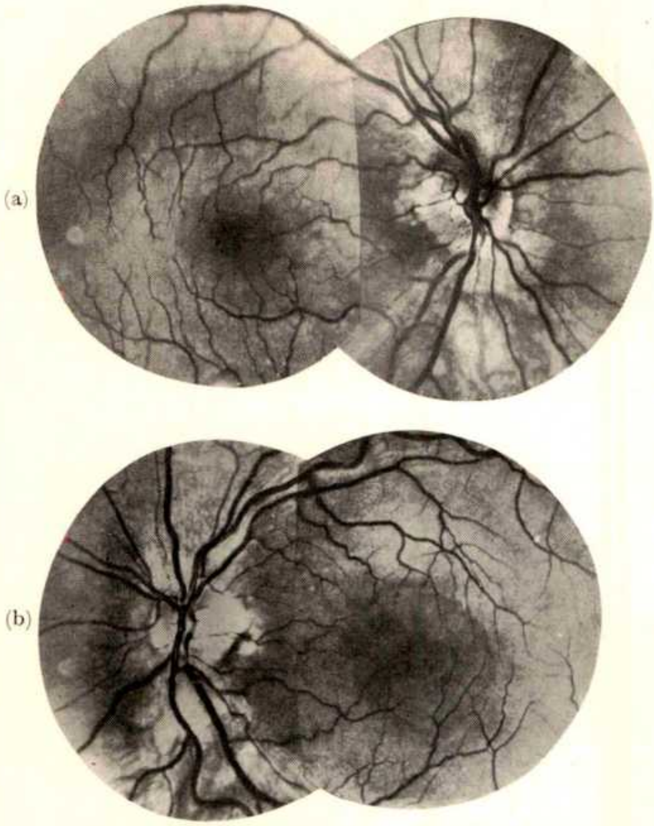

FIG. 1 (a) *Right eye, showing a few small perifoveal exudates.*

(b) *Left eye, showing large raised plaque of oedema over the entire macular area.*

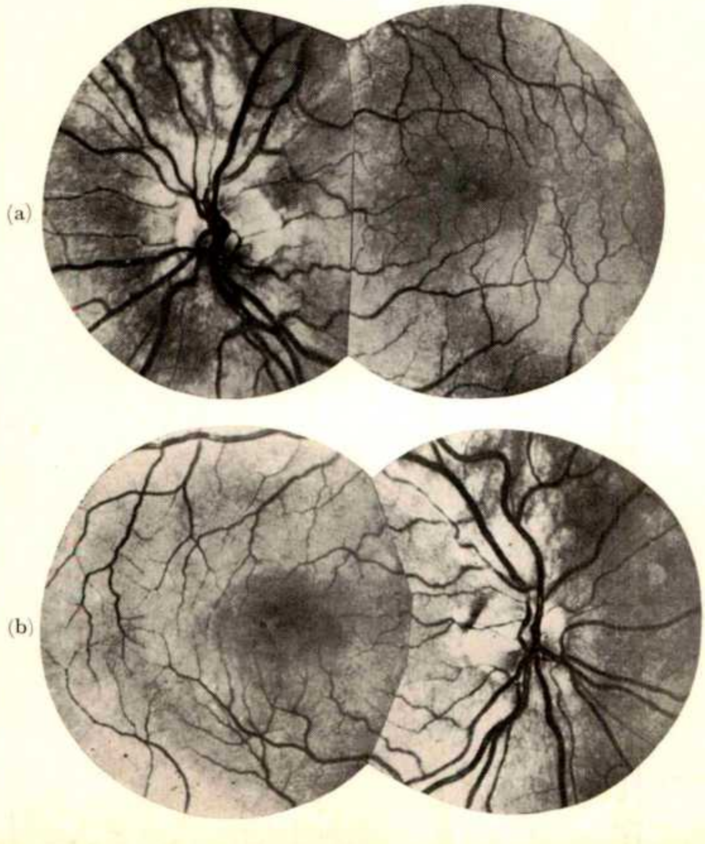

FIG. 2 (a) *Right eye 6 months after cessation of treatment.*

(b) *Left eye, showing fine macular pigmentation.*

in a patient with Reiter's syndrome after treatment with large doses of systemic corticosteroids. In the present case the coincidental development of bilateral macular exudates during treatment with very large doses of depot tetracosactrin and their rapid improvement after a reduction in dosage also suggests the possibility of iatrogenic disease, although the spontaneous development of an unrelated presenile macular dystrophy cannot be entirely ruled out. There was no family history of macular degeneration and the only other drug being taken by the patient when visual symptoms developed was dextropropoxyphene, which is not known to have ocular side-effects.

Fluorescein photography (Fig. 3) demonstrated a perifoveal leak in the choroidal circulation, but the exact pathogenesis of these lesions is uncertain. It is of interest that the patient was receiving excessive doses of depot tetracosactrin in error and that his symptoms improved rapidly when the dosage was reduced but the drug was not entirely withdrawn. The high dosage depot tetracosactrin resulted in weight gain, pigmentation, transient hypokalaemia and hyperglycaemia with glycosuria, but not in hypertension or peripheral oedema. The relationship of these corticosteroid side-effects, if any, to the development of a maculopathy is obscure.

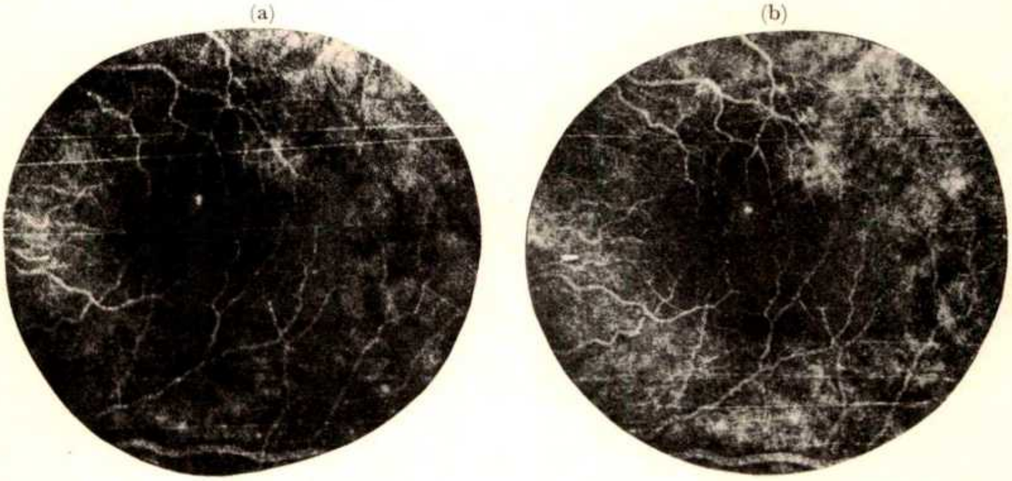

FIG. 3 *Left eye* (a) *fluorescein after 3 minutes.*

(b) *after 5 minutes, showing perifoveal leak in choroidal circulation.*

Summary

A 45-year-old man with an 18-months' history of rheumatoid arthritis developed bilateral macular lesions while receiving tetracosactrin in excessive dosage. Reduction in dosage was accompanied by spontaneous regression of the lesions, which suggests the possibility of an iatrogenic aetiology.

We wish to thank Dr. W. Watson Buchanan, Consultant Physician at the Centre for Rheumatic Diseases, for allowing details of this patient's case to be published.

We are indebted to Mr. Ibbott, Senior Optician, Southern General Hospital, for fundus photographs and to Mr. J. Watt, Tennent Institute of Ophthalmology, Western Infirmary, Glasgow, for the fluorescein photographs.

One of us (G.N.) is in receipt of a CIBA Clinical Research Fellowship.

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Brit. J. Ophthal. (1970) **54**, 410

"Contact lens" cornea in rheumatoid arthritis

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Peterborough District Hospital

It has been noted that patients suffering from long-standing rheumatoid arthritis often display a characteristic corneal lesion.

This consists of a partial opacity of the periphery of the cornea involving part or all of its circumference. The cornea in this area is thinned, usually by about a third of its normal thickness and has a well-demarcated central edge. It is minimally vascularized by superficial vessels crossing the limbus. The appearance is quite striking even upon superficial examination and resembles that of an eye wearing a microcorneal contact lens, so much so that it could well be called "contact lens" cornea (Fig. 1).

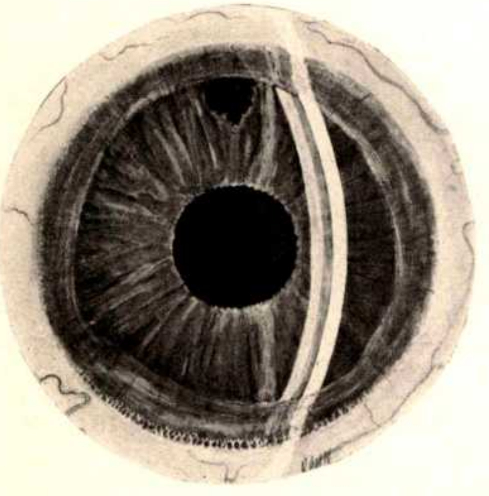

FIG. 1 *Drawing of slit-lamp appearance of cornea in the cases described (the lesion at 12 o'clock is a benign melanoma of the iris)*

Five cases illustrating the clinical features referred to are summarized in the Table (opposite).

Case reports

Case 1, a woman aged 70 years, had experienced soreness of both eyes from time to time over the last 10 years, not severe enough to warrant seeking medical advice. She had suffered from rheumatoid arthritis for 30 years with severe joint deformity, and had been treated with salicylates only. She attended the clinic because the right eye had been sore for 5 weeks.

Examination

Both eyes showed an annular opacity extending 2 or 3 mm. inwards from the limbus. The right eye showed slight injection, but there was no staining after the instillation of fluorescein. There was a small area of scleral thinning at 12 o'clock on the right eye. The visual acuity was 6/6 in each eye, the media clear, and the fundi normal. There was no evidence of uveitis either past or present.

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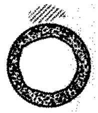
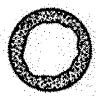
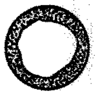
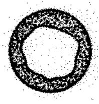
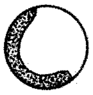
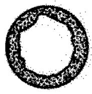
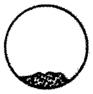
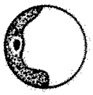
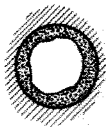
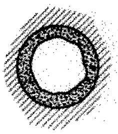
Table *Summary of five cases described*

Case no.	*Age (yrs)*	*Sex*	*Duration of RA (yrs)*	*Glaucoma*	*Eye*	
					Right	*Left*
1	70	F	30	–		
2	64	F	20	–		
3	62	F	13	–		
4	62	F	7	–		
5	56	M	17	+		

Eye lesions
▓ Corneal opacity
▨ Scleral thinning

Treatment

The symptoms resolved rapidly upon treatment with local mydriatics and steroids, and the appearance of the eyes was the same when the patient was reviewed 2 years later.

Full examination for glaucoma with applanation tonometry and Bjerrum screen testing showed no abnormality and the tear secretion was normal.

Case 2, a woman aged 64 years, was referred by a rheumatologist who had thought the appearance of the eyes was abnormal when she attended for treatment of arthritis. She had had minimal soreness of both eyes from time to time. Rheumatoid arthritis had been present for 20 years with severe joint deformity.

Examination

Both eyes had the characteristic ring of opacity involving the periphery of the cornea with slight superficial vascularization (Fig. 2, overleaf). The visual acuity of each eye was 6/9 after refraction. There was no evidence of glaucoma or uveitis, and tear secretion as tested by Schirmer's test papers was normal.

Result

The appearance of the eyes was unchanged when the patient was reviewed 6 months later.

(a) (b)

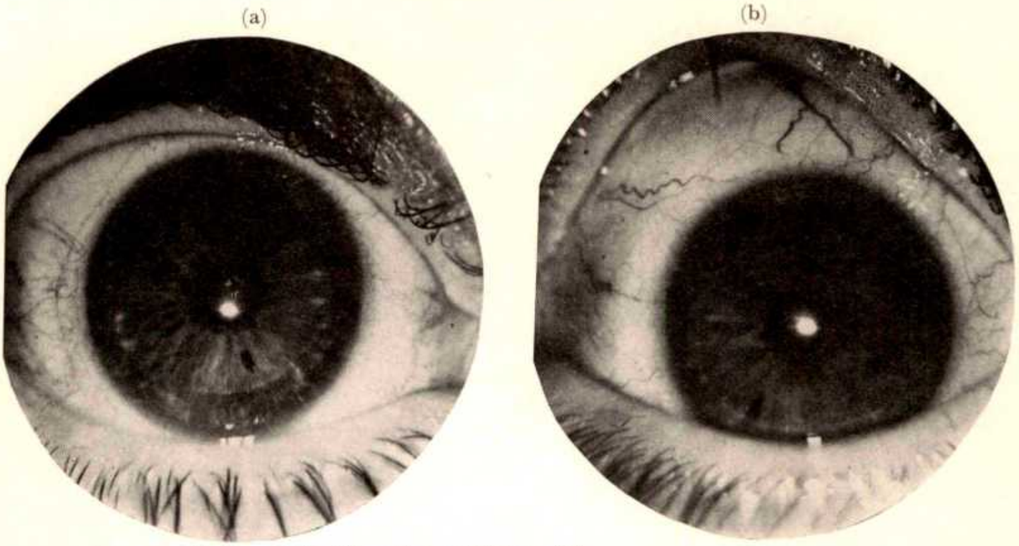


FIG. 2 *Case 2. Photograph of right eye* (a) *and left eye* (b)

Case 3, a woman aged 62 years, attended because of pain in the right eye for the previous month. She had had similar symptoms in a milder form from time to time which had resolved with treatment by drops prescribed by her doctor. She had suffered from rheumatoid arthritis for 13 years with multiple joint deformities.

Examination

The right eye showed the characteristic band of opacity on the cornea extending from 5 o'clock to 12 o'clock. The central edge of the opacity stained with fluorescein at 9 o'clock (Fig. 3).

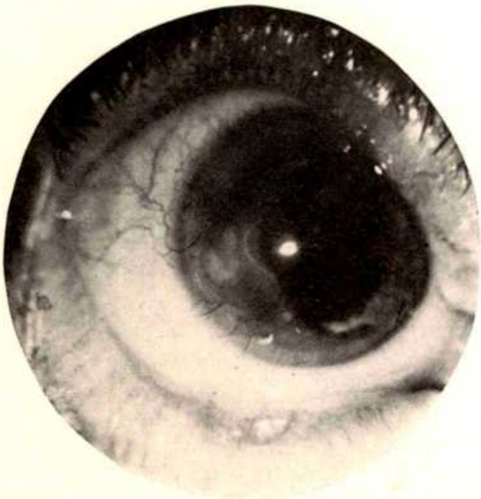


FIG. 3 *Case 3. Photograph of right eye, showing staining area*

The left eye showed the same type of opacity extending all round the peripheral cornea, but there was no staining point on this eye. The visual acuity was 6/18 in each eye, the decreased vision being due to lens opacities. There was no sign of uveitis or glaucoma and the tear secretion was normal.

Treatment

The staining area healed within 6 weeks after treatment with local steroids and mydriatics.

Case 4, a woman aged 62 years, had suffered from recurrent corneal ulceration of the left eye for about 4 years. The symptoms usually lasted for 3 months or so and resolved upon treatment with local mydriatics and steroids. There had never been any inflammation in the right eye. She had had rheumatoid arthritis for 7 years, and had been treated with salicylates only. The last and most severe attack had lasted for 3 months and showed no sign of resolving.

Examination

The visual acuity was 6/9 in each eye. The right eye showed a small area of opacity at 6 o'clock. The left eye displayed a ring of opacity on the cornea extending from 5 o'clock to 12 o'clock. It was 3 mm. or so in width and at a descemetocele was present at 9 o'clock (Fig. 4).

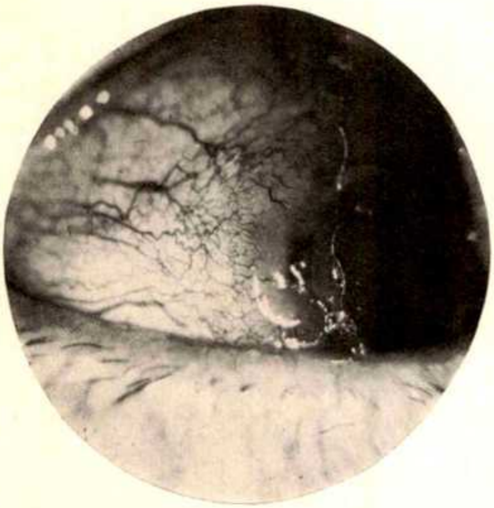


FIG. 4 *Case 4. Photograph of left eye, showing a descemetocele at 9 o'clock*

Treatment

It was felt that perforation of the left eye was likely in the weakened area, and an annular penetrating graft was therefore performed. The cornea healed without incident and corneal thickness has been maintained with no further episodes of ulceration in the 6 months follow up. Schirmer's test showed absence of tear secretion.

Case 5, a man aged 56 years, had experienced recurrent soreness of both eyes for several years, not severe enough to warrant seeking medical advice. He had rheumatoid arthritis of 17 years' duration and could walk only with the aid of crutches.

Examination

The visual acuity was 6/6 in each eye after refraction, with a moderate degree of myopia. Both eyes showed the typical annular opacity extending completely around each cornea, and there was also extensive scleral thinning all round in both eyes. Applanation tonometry showed that the ocular tension was 31 mm. Hg in the right eye and 58 mm. Hg in the left. The central fields on Bjerrum screen testing with a 2 mm. object showed no field loss and the discs did not appear to be cupped, although they were difficult to assess because of the myopic changes present. Gonioscopy showed open angles of medium width with no peripheral anterior synechiae.

Treatment

The patient was treated with miotics which controlled the raised ocular tension until his death a few months later.

Differential diagnosis

The relative lack of pain and acute inflammatory appearance differentiates this type of marginal ulceration from the necrotizing sclero-keratitis seen in association with the connective tissue diseases, most commonly with polyarteritis nodosa. This condition is acutely painful, causes rapid loss of corneal substance, and responds only to high doses of systemic steroids.

Terrien's marginal ulceration usually affects the superior cornea and usually has a more marked inflammatory element.

Senile marginal degeneration usually affects the interpalpebral area and does not often extend completely round the periphery of the cornea.

A very similar appearance on superficial examination may be seen in uveo-keratitis with sclerosing keratitis; this is illustrated by the two following patients:

(A) A woman aged 59 years had suffered from recurrent anterior uveitis for approximately 27 years and had herself noted a white ring surrounding both corneae for the past 5 years. Superficial examination showed an appearance very similar to that of Case 5, with the "contact lens" cornea surrounded by scleral thinning, but slit-lamp examination revealed that the opacity involved the posterior third of the cornea and was accompanied by deep vascularization. This patient had in addition numerous peripheral anterior synechiae in both eyes and had been treated for glaucoma for several years. She had had an iridectomy performed upon the right eye. Both discs were cupped and the visual fields considerably contracted.

Extensive investigations for rheumatoid arthritis, including serology and *x*-ray examination of the small bones of the hands and feet, were all negative.

(B) A woman aged 42 years had suffered from attacks of inflammation in both eyes lasting for several weeks at a time for many years. She had also been treated on one occasion for "acute" glaucoma. The visual acuity was 6/6 in each eye and both showed a white ring involving the periphery of the cornea. There was no scleral thinning but there was mild activity in both anterior chambers. Again, the slit lamp showed that the opacity involved the posterior third of the corneal thickness and that the superficial cornea was not affected. It is interesting to note that this patient also had numerous peripheral anterior synechiae causing raised intraocular pressure in each eye with accompanying visual field loss and cupping of the disc. She had had glaucoma surgery performed upon both eyes.

Discussion

Although rheumatoid arthritis is known to be accompanied by deficiency of lacrimal secretion and the corneal changes resulting therefrom and may also be accompanied by the various types of scleritis (Lyne and Pitkeathly, 1968), there are few accounts of corneal changes similar to those described above. Case reports of marginal furrows, which are almost certainly the same entity, include those of Brown and Grayson (1968), Frasca (1958), and Collier (1952).

Brown and Grayson described nine cases of marginal furrows of the cornea affecting patients suffering from rheumatoid arthritis of more than 5 years' duration. The furrows were seen most commonly at the inferior aspect of the limbus and were bilateral in four of the patients. Only one of their cases corresponded at all closely to those above in being circumcorneal. Inflammation and vascularization were minimal.

Four of the five patients in my series were women, and the average age was the middle sixties. This is to be expected in view of the association with rheumatoid arthritis, which is itself more common in women than men, and in which average age at onset is the middle thirties.

The mechanism of development of these lesions is not easy to explain. They may be due to the circumferential extension of a "dellen". These lesions consist of a shallow oval ulcer about 1·5 × 2 mm. in size accompanying a limbal swelling due to any cause.

Barraquer (1965) suggested that they were due to a discontinuity of the tear film caused by elevation of the lid by the limbal swelling and leading to desiccation of the cornea adjacent to it. From my own observations of these lesions, I am inclined to doubt the existence of the dry spot which I have been unable to demonstrate on the slit lamp. On the contrary there is usually a pool of fluid present which tends to stagnate as shown by the persistence of fluorescein in that situation when instilled, and it may be that lack of exchange of metabolites is the cause. It is likely that a pterygium results from the recurrent breakdown and healing of a "dellen", advancing a little further after each episode as Barraquer suggests. If, instead of progressing centrally, the "dellen" occurred at different points upon the limbus, an appearance similar to the "contact lens" cornea could be produced.

On balance, however, it seems more probable that the circumcorneal breakdown is due to a deficiency in the perilimbal vascular supply. It is known that the collagen of the sclera undergoes changes in scleritis associated with rheumatoid arthritis, accompanied by varying degrees of inflammation. It is known also that the arterioles are affected in rheumatoid arthritis, both generally throughout the body and in the eye. So far there has been no opportunity to examine an eye with this type of corneal lesion histologically.

Summary

A peripheral corneal opacity of a distinctive character involving the anterior third of the corneal thickness, was seen in five patients suffering from long-standing rheumatoid arthritis. The opacity was present over the whole of the circumference of the peripheral cornea in the majority of the eyes affected and the condition was bilateral to some degree in all five patients.

Inflammation and vascularization were minimal.

I wish to thank the consultants of the Manchester Royal Eye Hospital for allowing me to describe their case and Mr. R. Neave of the Department of Medical Art, University of Manchester, for the slit-lamp drawing.

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Glaucoma in the Hallermann-Streiff syndrome

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The Hallermann-Streiff syndrome is a complex association of developmental anomalies principally involving structures of ectodermal origin. The constant expressions of the syndrome are dyscephaly with mandibulo-facial malformation, bilateral congenital cataracts, and dental anomalies, while hypotrichosis, cutaneous atrophy, microphthalmos, and proportionate dwarfism are frequently present (Table I) (Ponte, 1962). Numerous inconstant ocular features have been described, including anti-mongoloid palpebral fissures, blue sclerae, keratoglobus, malformation of the drainage angles, peripheral anterior synechiae, iris atrophy, persistent pupillary membrane, posterior synechiae, membranous cataract, amorphous retrolenticular membrane, vitreous opacities, pale optic discs, colobomata at the optic nerve entrance, retinal folds, various atrophic chorio-retinal changes and glaucoma (Table II) (Ludwig and Korting, 1950; François, 1958; Falls and Schull, 1960; Wolter and Jones, 1965; Ide and Webb, 1969).

Table I *Main features of the Hallermann-Streiff syndrome.*

A. Constant	*B. Frequently present*
1. Dyscephaly with mandibulo-facial malformation	4. Hypotrichosis
2. Bilateral congenital cataracts	5. Cutaneous atrophy
3. Dental anomalies	6. Microphthalmos
	7. Proportionate dwarfism

Table II *Inconstant ocular features of the Hallermann-Streiff syndrome.*

1. Anti-mongoloid palebral fissures
2. Blue sclerae
3. Keratoglobus
4. Malformation of the drainage angles
5. Peripheral anterior synechiae
6. Iris atrophy
7. Persistent pupillary membrane
8. Posterior synechiae
9. Membranous cataract
10. Amorphous retrolenticular membrane
11. Vitreous opacities
12. Pale optic discs
13. Colobomata at optic nerve entrance
14. Retinal folds
15. Atrophic chorio-retinal changes
16. Glaucoma

It is the purpose of this communication to describe two patients who have the classical manifestations of the Hallermann-Streiff syndrome with glaucoma, and to discuss the aetiology, prevention, and therapeutic problems of this complication.

Case Reports

Case 1. A Caucasian male born at term in June, 1967, after a normal pregnancy, weighed 4 lb. 10 oz. at birth. There was no family history of hereditary disorder and the unrelated parents, who were born in 1936, are both healthy. There was one previous stillbirth in 1961, of which no details

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1. *Brit. J. Ophthal.* (1955), **39,** 557
2. *Brit. J. Ophthal.* (1956), **40,** 159
3. *Brit. J. Ophthal.* (1965), **49,** 98

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Reigate	25 Church Street, Reigate, Surrey	Reigate 43577
Richmond	7 Lichfield Terrace, Sheen Road, Richmond, Surrey	01-940 3515
Rustington	8 Churchill Parade, The Street, Rustington	Rustington 6330
Wimbledon Bdy.	70 Broadway, London, S.W.19	01-542 4916
Stirling	34 Port Street, Stirling, Scotland	Stirling 2864
Sunderland	204 High St. West, Sunderland, Co. Durham	Sunderland 70625
Twickenham	36 Heath Road, Twickenham, Middlesex	01-892 9543
Victoria	52 Sloane Square, London, S.W.1	Sloane 7900
Wandsworth	67 East Hill, London, S.W.18	01-874 2187
Waterloo	191 Waterloo Road, London, S.E.1	01-923 5343
Welling	35 Bellegrove Road, Welling, Kent	01-303 8908
Wimbledon	84 High Street, London, S.W.19	01-946 5533
Worthing	Revenue Buildings, Chapel Road, Worthing	Worthing 201856

are available. There are no siblings. The infant was first seen in the Eye Department at the age of 5½ months, when he was found to have the characteristic features of the Hallermann-Streiff syndrome (Table I). Dense bilateral cataracts obscured all view of the ocular fundi. A discission operation was carried out on the right eye at the age of 7 months and a red reflex was reported in this eye 2 weeks later. The left cataract absorbed spontaneously between the ages of 8 and 13 months. No ocular inflammation was observed.

The infant was kept under frequent observation and was re-admitted for further assessment at the age of 17 months. At this time his height was 24·5 in., and he weighed 12 lb. 11 oz., both measurements below the third percentile for his age. There was fronto-parietal bossing, hypoplasia of the mandible and maxilla, and a small beak-like nose. The teeth were delayed and irregular in eruption and the ears showed a vestigial antitragus. There was cutaneous atrophy, especially evident on the face at the bridge of the nose where the subcutaneous veins were particularly prominent. The hair on the scalp was fair and rather sparse. Optokinetic responses were elicited in each eye and the peripheral fields were full to large fixation targets. The eyelashes and brows were absent. There was pendular nystagmus and a marked alternating squint with limited abduction of each eye. The paralimbal sclera was greyish-blue and the corneae were bright and clear (see Figs 1 and 2).

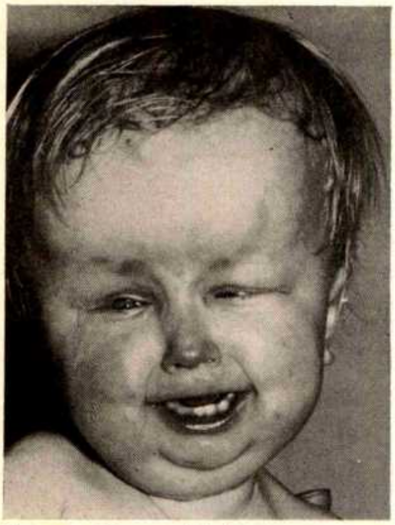

FIG. 1 *Case 1, full face*

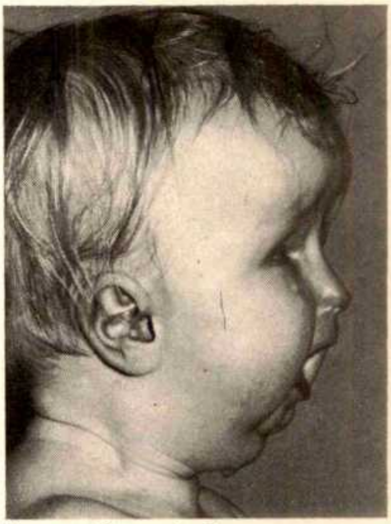

FIG. 2 *Case 1, profile*

Examination under anaesthesia revealed that the right horizontal corneal diameter measured 9·0 mm. and the left 9·5 mm. The intraocular pressures were 26 mm. Hg in the right eye and 36 mm. Hg in the left (Schiötz tonometer 7·5 g. wt). The anterior chambers were clear and deep centrally, but gonioscopic examination revealed that the drainage angles were closed in all meridians of both eyes by peripheral anterior synechiae. The irides were greyish-blue and atrophic and there was a small degree of iris *bombé* in each eye. Both pupils were irregular and dilated only slightly with cyclopentolate 1 per cent. Fine strands of persistent pupillary membrane extended from the collarettes to lenticular capsule remnants, and there were multiple posterior synechiae in both eyes. There were good red reflexes in each eye, and ophthalmoscopic examination revealed coarse granular mottling in the equatorial regions. There was a retinal fold projecting from the lower temporal quadrant to the paramacular area of the right eye.

After 2 weeks' administration of acetazolamide (Diamox) 10 mg./kg. body weight /24hrs a further examination under anaesthesia was carried out. The intraocular pressures were 23 mm. Hg in the right eye and 26 mm. Hg in the left (Möller hand-held applanation tonometer). Since that time the intraocular pressures have remained around this slightly elevated level.

Case 2. A Caucasian female born at term in May, 1936, after a normal pregnancy. There was no family history of any hereditary disorder and the unrelated parents are both healthy. The mother was born in 1909, and the father in 1905. There was a stillbirth in 1938, of which no details are available. There are no siblings. The patient was first seen in the Eye Department at the age of 3 months, and exhibited the characteristic features of the Hallermann-Streiff syndrome (Table I). Discission operations were carried out on each eye at the age of 5 years. Postoperatively the corrected vision was recorded as 5/50 ('E' test) in each eye. At the age of 22 years the patient returned to the hospital complaining of deterioration in the vision of the right eye. The corrected vision was then hand movements in the right eye, and 4/60 in the left. The intraocular pressures were 41 mm. Hg in the right eye and 31 mm. Hg in the left (Schiötz tonometer 10 g. wt.). Miotic therapy failed to reduce the pressures, and a right trephine operation was carried out and repeated without success 4 months later. This was followed by a right cyclodiathermy operation in a further 9 months, but the visual acuity in the right eye deteriorated to bare perception of light while in the left eye the visual acuity was maintained at 4/60, with a full peripheral field to confrontation, in spite of poor control of the intraocular pressure which ranged between 25 and 45 mm. Hg (Schiötz tonometer 10 g. wt.). The left optic disc was reported to be pale and cupped. At the age of 28 years the patient developed a granulomatous anterior uveitis in the left eye and the pressure became still higher, ranging between 40 and 70 mm. Hg (Goldmann applanation tonometer). The uveitis settled, but the intraocular pressure failed to respond to treatment with local miotics and systemic acetazolamide (Diamox). A left trephine operation was carried out, and repeated without success 10 months later. This was followed by a left upper nasal quadrantic cyclodialysis in a further 2 months. The medical therapy was continued but the pressure still remained high, between 20 and 40 mm. Hg (Goldmann applanation tonometer).

The patient was examined in this department at the age of 32 years. She was of normal intelligence and small proportionate stature. Her height was 53 in. and she weighed 91 lb. There was marked brachycephaly with frontal bossing and hypoplasia of the mandible. The nose was beak-like and the antitragus of both ears was very small. The dentition was irregular and there were several persisting deciduous teeth. The skin was thin and atrophic and the hair on the scalp was sparse (see Figs 3 and 4).

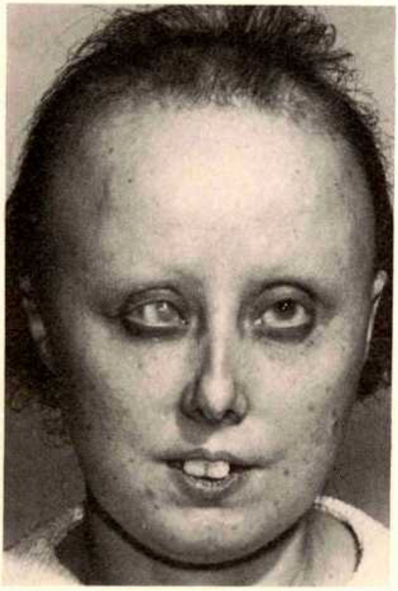

FIG. 3 *Case 2, full face*

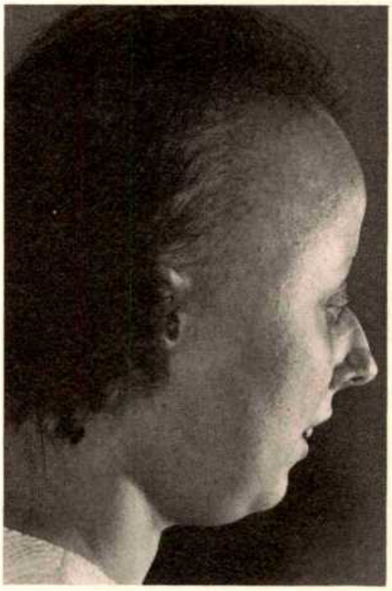

FIG. 4 *Case 2, profile*

The patient's corrected vision was perception of light in the right eye and counting fingers at 1 ft. in the left. The projection of light in the right eye was poor and the left peripheral field showed gross constriction to confrontation. The eyebrows and lashes were scanty. There was pendular nystagmus and a marked right convergent squint. There were extensive bilateral ciliary staphylomata. The right cornea was ectatic and oedematous with large epithelial bullae. The left cornea was less oedematous with fine epithelial bullae and there were crenated keratic precipitates. The right and left transverse corneal diameters measured 9·5 mm. The intraocular pressures were 45 mm. Hg in the right eye, and 25 mm. Hg in the left (Goldmann applanation tonometer). The state of the right cornea precluded any further assessment of the eye.

The left anterior chamber was deep centrally and showed a mild flare with occasional cells. Gonioscopic examination revealed that the drainage angle was closed off by peripheral anterior synechiae in all but the upper nasal quadrant, where the cyclodialysis had been carried out. Here the angle appeared open with multiple coarse strands of iris tissue extending across to the region of Schwalbe's line. The iris was greyish-blue and atrophic. The collarette was ill-defined and strands of persistent pupillary membrane extended to lenticular capsule remnants. There were multiple posterior synechiae. A red reflex was present, but fundus detail was poorly defined.

During the past 6 months the patient has been instilling adrenaline bitartrate 1 per cent. (Eppy) twice daily into the left eye, in addition to miotics and systemic acetazolamide (Diamox). The left intraocular pressure has fallen to within normal limits, ranging from 12 to 17 mm. Hg (Goldmann applanation tonometer). The epithelial bullae have cleared, and the anterior chamber remains quiet. The vision has improved slightly to counting fingers at 2 ft.

Discussion

In view of the findings in these two patients it was interesting to discover that only a small minority of the patients with the Hallermann-Streiff syndrome reported in the literature were found to have glaucoma. A short review of some of these patients is therefore relevant.

The most fully documented patient with the Hallermann-Streiff syndrome and glaucoma has been reported by several authors over the past 23 years (Moehlig, 1946; Falls and Schull, 1960; Wolter and Jones, 1965).

This male patient was born 2 months prematurely in July, 1938, and weighed 3 lb. 2 oz. The mother noticed what appeared to have been a spontaneous rupture of the cataractous left lens at the age of 18 months. He was first reported at the age of 3 years, when he was found to have nystagmus, a left divergent squint, a right congenital caratact, and left aphakia. A right discission operation was carried out under general anaesthesia at this age, and the lens matter was said to have dissolved satisfactorily in a quiet eye. At the age of 8 years, he was reported to have a left divergent squint, bilateral microphthalmos and aphakia, normal anterior chambers, round central pupils, clear media, and normal fundi.

Iridocyclitis with intermittent glaucoma developed in the left eye at the age of 20 years. This failed to respond to local atropine and steroids, and the blind painful left eye was enucleated in 1964. Histological examination revealed a closed anterior chamber angle with newly formed Descemet's membrane extending around the false angle onto the anterior iris surface. The empty lens capsule was attached to the iris pigment epithelium, and was ruptured in its anterior aspect. Granulomatous inflammatory reaction with epithelioid and giant cells extended from the ciliary body and iris to the anterior rupture in the rolled-up lens capsule. There was extensive retinitis proliferans, a retinal detachment, and marked atrophy of the optic disc and optic nerve.

Wolter and Jones (1965) commented that the granulomatous reaction around the remaining lens capsule suggested that the chronic iridocyclitis may have been due to hypersensitivity to the cataractous lens substance.

The first patient described by Hallermann (1948) had total bilateral congenital cataracts.

At the age of 7 months a discission operation with anterior chamber wash-out was performed on the left eye, and at 3 years of age the cataract in the right eye absorbed spontaneously. After this the right eye was apparently quiet, but the patient was later found to have posterior synechiae and secondary glaucoma. A superior iridectomy operation was performed to relieve the secondary glaucoma. When reviewed at the age of 22 years the right eye was blind and the intraocular pressure considerably raised. The corrected visual acuity of the left eye was 5/35 and the intraocular pressure was normal.

Streiff (1950) described a female patient who was born 2 months prematurely and according to the parents could not see as a child.

At the age of 18 years the patient was seen by Professor Streiff's father, who found bilateral microphthalmos and total congenital cataracts and performed a discission operation on each eye. The visual acuity in the right eye improved to counting fingers, but after a year secondary glaucoma occurred in each eye and vision was lost. When this case was reviewed 12 years later the patient, now aged 31, had raised intraocular pressure in each eye and there was glaucomatous cupping of the right optic disc, but vitreous opacification obscured the view of the left fundus. No evidence of active intraocular inflammation or sequelae of intraocular inflammation had been observed in the anterior segments of the eyes (personal communication).

Ullrich and Fremerey-Dohna (1953) reviewed a 2½-year-old girl with the syndrome who had bilateral microphthalmos, cataract, and posterior synechiae.

The intraocular pressures were recorded as 30 mm. Hg in the right eye and 40 mm. Hg in the left. Multiple discission operations were performed on both eyes, and a good view of the fundus was obtained. Aphakic spectacles were fitted and the child could see, but no accurate estimate of visual acuity was possible. No further mention was made of the intraocular pressures.

A patient with a particularly interesting ocular history who represents a forme fruste of the syndrome, having all the features listed in Table I but congenital cataracts, was reported by Schondel (1943) and Gregersen (1956).

The patient's visual acuity was recorded as counting fingers at 0·5 m. at the age of 5 years, and the pupils dilated poorly with atropine. At the age of 12 years there was nystagmus, a convergent squint, and marked microphthalmos. The corneal diameters measured only 8 mm. Fine keratic precipitates were present, and the irides were funnel-shaped, reminiscent of iris *bombé*. The pupils contained cicatricial remnants of exudate adherent to the anterior lens surface. Red reflexes were present, but no accurate fundus detail could be seen because of the nystagmus. Between the ages of 15 and 25 years, spontaneous membranous conversion of the lenses occurred. At the age of 30 yearf glaucoma developed in the right eye. This was tolerably controlled by the administration os acetazolamide (Diamox) and pilocarpine. The corrected visual acuity was recorded as 1/18 and 1/24.

The abnormalities which are likely to cause an elevation of intraocular pressure in the Hallermann-Streiff syndrome have two possible origins. They may be developmental anomalies or complications and sequelae of intraocular inflammation. Duke-Elder (1964) stated that, in microphthalmos, the development of glaucoma is a relatively common occurrence, depending presumably upon the smallness of the cornea, the relatively great size of the lens, and the presence of persistent embryonic tissue in the angle of the anterior chamber. In the patients with the Hallermann-Streiff syndrome, microcornea is one of the salient features, but glaucoma usually occurs in most patients after the lens has been needled or undergone spontaneous rupture. The only description of malformation of the anterior chamber angle appears in the report of Ludwig and Korting (1950), but they did not specify the type of malformation. However, the evidence of intraocular inflammation in the syndrome is strong and where glaucoma has occurred there have almost invariably been signs of uveitis or its sequelae. Our second patient had particularly uncontrollable glaucoma when the anterior uveitis was active and both patients had posterior and peripheral anterior synechiae. Of the five patients with glaucoma reviewed from the literature, the case described by Streiff (1950) was exceptional in that there was no evidence of intraocular inflammation or its sequelae. The inflammation is typically a granulomatous anterior uveitis, and occurs in the majority of patients where there has been surgical or spontaneous release of the lens matter into the anterior chamber. This is compatible with the suggestion of Wolter and Jones (1965) that the uveitis may represent a hypersensitivity reaction to cataractous lens substance.

There is clearly a better prognosis with surgical discission than with spontaneous cataract absorption. This is apparent in the patient described by Moehlig (1946), Falls and Schull (1960), and Wolter and Jones (1965), and in the patient described by Hallermann (1948). These two patients had a discission operation performed on one eye with a fair result, but spontaneous cataract absorption occurred in the other eye, which became glaucomatous and blind. The reports from Gregory (1955) and van Balen (1961), each describing two patients who had bilateral discission operations with satisfactory results, support this observation. However, the patient who underwent bilateral discissions at 18 years of age (Streiff, 1950) and our second patient show that cataract surgery does not eliminate the hazard of glaucoma.

Therefore it appears preferable to operate on the cataracts of both eyes of these patients as soon as possible, thus avoiding spontaneous cataract absorption and suppression amblyopia. Postoperative reviews must be frequent and regular to ensure that if intraocular inflammation occurs it is diagnosed and treated promptly. The ophthalmic surgeon should not delay intervention in the hope that spontaneous cataract absorption will occur in a difficult microphthalmic eye, as the prognosis is worse and he has no control over the timing of the event.

The onset of glaucoma in patients with the Hallermann-Streiff syndrome presents a most difficult therapeutic problem. Our limited experience indicates that medical treatment with local miotics and systemic carbonic anhydrase inhibitors is the most advantageous. Gregersen (1956) used this combination with some success. The addition of adrenaline bitartrate 1 per cent. (Eppy) appears to have been particularly useful in our second patient. Surgical treatment has been unsuccessful. Hallermann (1958) performed a superior iridectomy to reduce intraocular pressure without success, and our second patient had numerous surgical procedures which failed to reduce the intraocular pressure.

Summary

Two patients with the Hallermann-Streiff syndrome who developed glaucoma are reported. Five similar patients are reviewed from the literature, and the aetiology, prevention, and therapeutic problems of the complication are discussed.

We should like to thank Mr. John Foster, Mr. Brian Martin, and Mr. Brian Harcourt for allowing us to study their patients, and for their advice and encouragement in writing this paper.

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Ruby laser transmission and the lens

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The earliest recorded study of the transmission of light by the ocular media is attributed to Aschkinass (1895), but according to Meyer-Schwickerath (1960) his method was grossly inaccurate. Luckiesh (1921) calculated the transmissivity of the ocular media on the basis that it equalled that of a layer of water 2·28 cm. thick. Shoji (1923) and Bücklers (1926) both made measurements of transmission but the wavelengths used were all below 400 mμ.

In a classic paper, Ludvigh and McCarthy (1938) estimated the transmission of light of wavelengths from 400 to 820 mμ to be 50 per cent. This paper is much quoted in the subsequent literature, and Davson (1963) quotes only the figure of 50 per cent. In fact Ludvigh and McCarthy based their estimate on experiments on only four eyes, all of which had been enucleated because they contained malignant melanomas. It can be reasonably argued that the ocular media may well have undergone pathological change while remaining clear to the naked eye.

The results of Ludvigh and McCarthy (1938) appear to have been accepted until 1951, when they were seriously questioned by Wald (1951). At that time Meyer-Schwickerath (1951), in developing his light-coagulator, became interested in the transmission of light by the ocular media; he repeated the experiments of Ludvigh and McCarthy (1938) and arrived at the same value of 50 per cent. However, he had no hesitation in discarding the results because the specimens used showed signs of *post mortem* change when examined critically.

Weale (1953), discussing the nature of light reaching the retinal elements after its passage through the ocular media, stated that "as far as the human eye is concerned, such knowledge is very inadequate in the case of the enucleated eye and non-existent in that of the eye *in situ*". Meyer-Schwickerath (1954) carried out further studies and calculated absorption values on the assumption that they were the same as that of 2·28 cm. water, quoting Goldmann, König, and Mader (1950) to justify this assumption. Such calculations showed that, at a wavelength of 694·3 mμ, transmission *via* the ocular media was about 95 per cent.

Wiesinger, Schmidt, Williams, Tiller, Ruffin, Guerry, and Ham (1956) studied the transmission of light *via* the ocular media of nine freshly-enucleated rabbit eyes, using a spectrophotometer operating from 380 to 1,400 mμ. Their results also showed that, in the 694·3 mμ range, transmission is of the order of 95 per cent. The technique appears to be free of major sources of error but, again, all the ocular media were grouped together in this study. There seems to be no work recorded in the literature in which the transmission of non-coherent light through the individual ocular media has been measured. Ham, Williams, Geeraets, Ruffin, and Mueller (1963) and Geeraets and Berry (1968) confirmed the figure of 95 per cent., again using non-coherent light. It may be concluded that the

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absorption of light in the lens alone is not more than 4 to 5 per cent. and presumably, since the lens is only one constituent of the ocular media, somewhat less.

There appears to be a universal assumption that the transmission of a laser beam through the ocular media is the same as that of a beam of light of the same wavelength. This may or may not be true, and an attempt has therefore been made to confirm this assumption by measuring the proportion of light energy from a ruby laser which is transmitted through the isolated lens.

Apparatus and methods

The lenses for these studies were all taken from healthy young adult rabbits. The following method of dissecting and mounting the lens was devised to preserve its optical properties by ensuring that it was not damaged or allowed to dry.

After enucleation the eye was washed, placed cornea downwards on filter paper, and held firmly with forceps by the stump of the optic nerve while four cuts were made in the sclera extending anteriorly to 1 mm. from the limbus. (This distance is important as the cornea must retain its shape in order to support the lens during the dissection.) The eye was then opened out as in Fig. 1, care being taken to avoid contact with the lens (Fig. 2). Incisions were made with a razor blade across the base of all four flaps 1 mm. peripheral to the ciliary body, and penetrating the retina and choroid but not the sclera; the peripheral remnants of retino-choroidal tissue were then discarded, the central remnants being pushed up to the ciliary body, and the whole dissection was immersed in a Petri dish of silicone (Midland Silicone 200/10 cSt). Pulling up one portion of the choroid allowed a small incision to be made in the ciliary body through to the anterior chamber. Using small scissors, the ciliary body was completely freed from the sclera. Great care was taken to prevent damage to the lens surface. The ciliary body/iris/lens preparation was then inverted on the cornea (Fig. 2), and the iris was cut into quadrants. These cuts were ended 2 mm. from the root of the iris to prevent the zonule from tearing. The quadrants were retracted and a suture passed through each

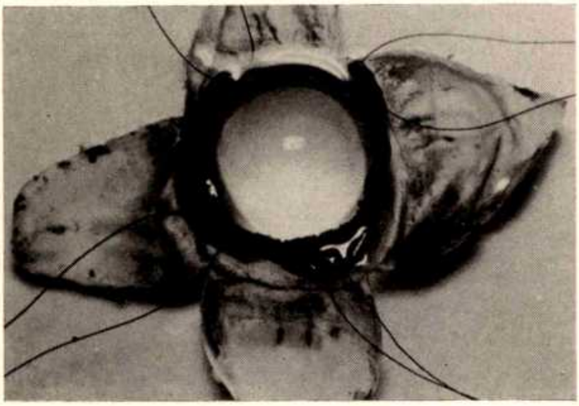

FIG. 1 *Dissected eye, showing lens preparation lying inverted in cornea with sutures in place in uvea*

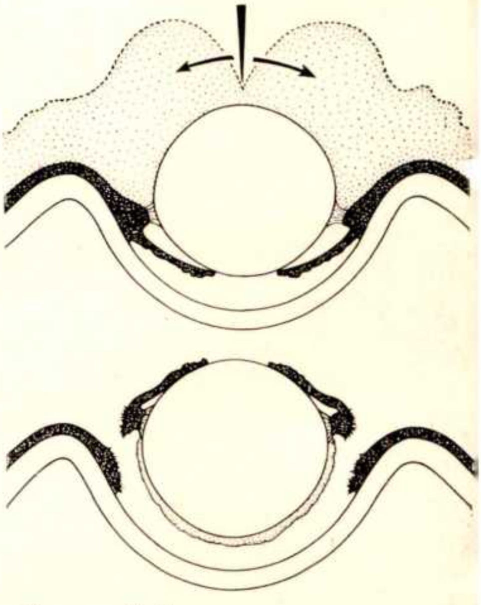

FIG. 2 UPPER *Method of removing bulk of adherent vitreous with a razor blade*
LOWER *Inverted lens lying in intact cornea. The remnants of the vitreous attached to the posterior surface f the lens are later removed*

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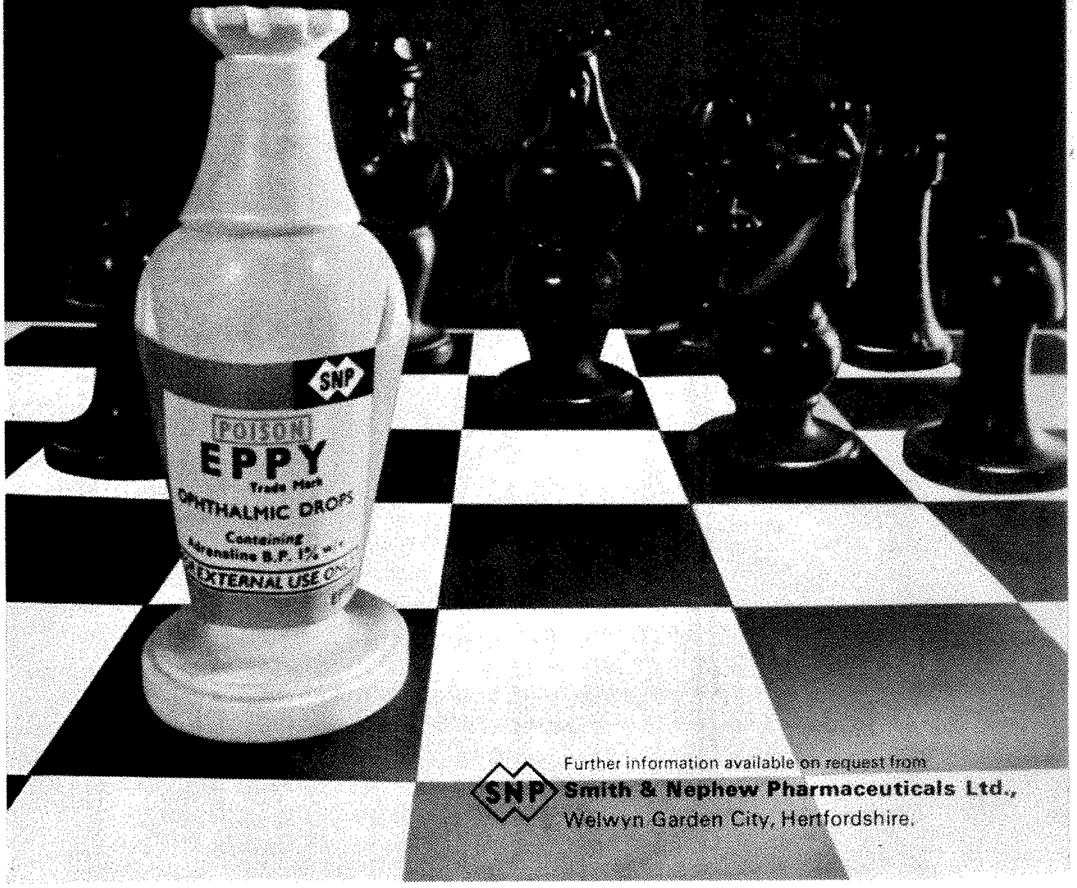

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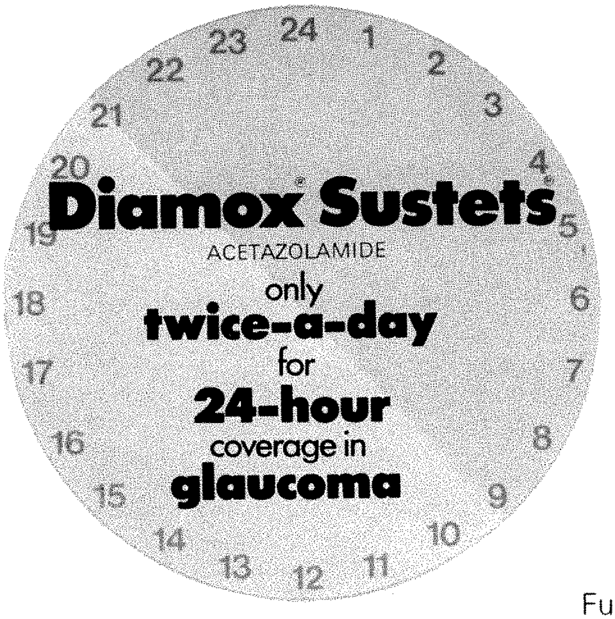

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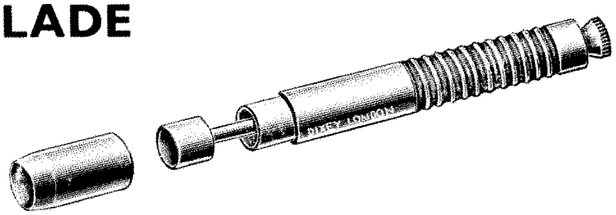

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(Fig. 1). A simple wire frame was clamped horizontally just above the preparation and the sutures were tied to each corner (Fig. 3). By touching the extreme periphery of the lens (now securely mounted in its frame) with a piece of filter paper and sweeping radially, the last of the vitreous was removed. The transparency of the lens could then be checked by slit-lamp inspection.

The lens was suspended in an optical cell having parallel front and rear surfaces and filled with silicone, thus avoiding any refraction or reflection at the lens surface. The cell was then positioned directly in front of a cone calorimeter (Laser Associates, Model 42) with an aperture of 24 mm. The ruby laser source was mounted on a Gambs photo-slit-lamp (Hallman, Perkins, Watts, and Wheeler, 1968) positioned in front of the cell; the lens surface was thus clearly visible, the smallest aperture of the illuminating system being used to indicate that portion of the lens to be traversed by the beam. The laser was fired six times through different parts of each lens; this was then removed and six shots were fired through the cell, now filled only with silicone. All shots were fired at fixed time intervals to avoid overheating of the ruby. The insertion of the preparation into the cell obviously reduced the optical path of the beam through the silicone by a distance equal to the thickness of the lens, but the absorption by this layer of silicone was found to be so small that it could be ignored.

The calorimeter had a sensitivity of 235 μV/J, and produced its peak voltage about 12 sec. after irradiation; in use, continuous recordings were made of its output for 20 sec. before and after firing the laser. By connecting the calorimeter to a circuit of constant resistance, it was possible to measure the current with an electronic galvanometer (John Fluke, Model 841A), giving a measure of the calorimeter output voltage. Calibration was done by incorporating a device in series with the galvanometer which generated a known voltage and also provided a means of zeroing the instrument by producing a constant but variable "backing-off" voltage. A continuous trace of the calorimeter's output and of the calibration signals was made possible by connecting an ultraviolet recorder to the galvanometer.

Results (see Table)

Experiment no.	*Calorimeter reading* (Mean of six exposures mJ)*		*Difference (per cent.)*	t-*test values*
	Without lens	*With lens*		
1	138·3	135·7	1·9	3·8
2	127·0	124·3	2·1	3·5
3	118·8	108·5	2·8	11·8
4	135·0	131·3	2·7	4·8
5	115·8	114·5	1·1	4·7
6	114·0	111·8	1·9	4·5
7	118·5	115·8	1·9	5·7
8	102·8	100·2	2·5	3·0
9	109·2	106·0	2·9	6·5
10	108·2	105·0	3·0	5·8
11	110·7	108·0	2·4	5·4
12	112·0	109·5	2·2	7·3
13	102·8	100·0	2·7	6·1
14	107·5	105·2	2·1	6·6
15	115·8	113·8	1·7	4·5
16	118·0	114·7	2·8	6·7
17	99·0	96·8	2·2	4·8
18	105·8	104·3	1·4	3·9
19	94·8	92·8	2·1	5·6
20	103·8	101·8	1·9	5·6
		Mean	2·2 per cent.	
		S.D.	±0·51	

* Comparison between readings with and without the lens using Student's *t*-test showed a significant difference at the 0·05 level in each experiment.

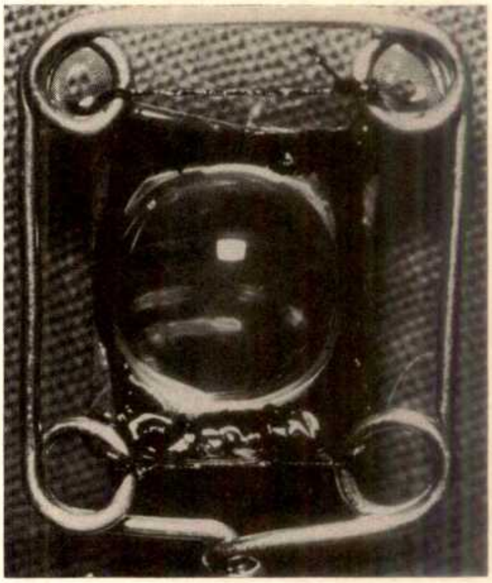

FIG. 3 *Completed preparation mounted in wire frame*

Discussion

In considering the accuracy of the transmission values obtained, it should be remembered that the output of any laser from shot to shot is variable, and that no facilities for monitoring the energy of each shot were available. The error arising from such variations was minimized by taking a mean of six readings of both values, but could not be completely excluded.

Khosla (1968), working in this Department and using similar methods to those employed here, found that the rabbit cornea absorbed 1·6 per cent. of light from a ruby laser beam. This value added to the 2·2 per cent. for the lens gives 3·8 per cent., leaving approximately 1·2 per cent. of the original 5 per cent. figure quoted for absorption in the ocular media. The remaining media, the aqueous and vitreous, if regarded as water would be expected to absorb about 1·2 per cent. of light at a wavelength of 694·3 μm.

The importance of the measurements obtained both in this study and in Khosla's work lies less in their absolute value (which could be measured more accurately using lower energy light sources and photoelectric measuring devices) than in the fact that together they differ little from figures produced by workers using non-coherent light sources. It would seem, therefore, that the absorption of light from a ruby laser by the rabbit lens is no greater than the absorption of ordinary red light. There is no reason to suppose that the human lens would behave differently.

No clinically visible effects on the lens have been observed with energies of 240 mJ, but this does not exclude the possibility of cellular damage as demonstrated in the cornea by Parr and Fisher (1967). There is no reason to suppose that the young normal human lens would behave differently, though more light would be absorbed by older lenses and those with opacities.

Summary

A technique for measuring *in vitro* the transmission of the rabbit lens to ruby laser light at 694·3 mμ is described. The mean absorption value was found to be 2·2 per cent. (S.D. ±0·51), suggesting that transmission figures derived from experiments using non-coherent light are also applicable to laser light.

We should like to thank Prof. E. S. Perkins for his valuable advice and encouragement, Mr. M. Bass for skilled technical assistance, and Mr. T. Tarrant of the Department of Audio-Visual Communications for the illustrations.

This work was aided by a grant from the Ministry of Defence.

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Brit. J. Ophthal. (1970) **54**, 428

Fixed vitreous cyst

M. JOYCE

Birmingham and Midland Eye Hospital

Vitreous cysts, which are rarely reported in the literature, tend to be described as small, transparent, mobile spheres causing transient blurring of vision (Cassady, 1939). The surfaces tend to be dimpled and irregularly pigmented. Details of the fundus can be clearly seen through their walls.

The great majority tend to be congenital in nature and associations with congenital remnants have been described on occasions, *e.g.* with the hyaloid artery (Koby, 1926).

However, vitreous cysts have been reported in association with diseased eyes, for example in cases of retinitis pigmentosa (Perera, 1936), and Duke-Elder (1964) felt that pathological cysts tended to be fixed, whereas congenital cysts were mobile or attached to pedicles. Occasionally such cysts are bilateral (Perera, 1936).

In the case reported here the cyst was fixed.

Case Report

A 26-year-old woman complained of sudden loss of the visual field in the left eye. She had suddenly become aware of a shadow in the upper field of vision. There was no previous history of ocular disease.

Examination

The visual acuity in the right eye was 6/5 and in the left eye 6/12 (refractive error +0·5 D sph. right and left).

The left eye contained a large fixed transparent globular cyst in the lower temporal quadrant of the vitreous. It extended from just below the macula to the ora serrata from 6.30 to 8.30 o'clock (Figure).

The wall was smooth and glistening and the retinal vessels and other details of the fundus could be seen clearly through it. No pigment was evident on the wall of the cyst. The rest of the media appeared normal.

Examination of the visual fields revealed an upper field loss consistent with the position of the cyst. The extent and appearance of the cyst has remained constant, as has the field loss, for a period of 6 months.

Discussion

As no case of vitreous cyst has been examined histologically their exact nature remains speculative. Undoubtedly the majority are developmental in nature, and their association with the hyaloid apparatus, lens capsule, and optic disc have shown this to be true. Cassady (1939) believed that the majority arose from the primary vitreous and certainly the primary vitreous is closely associated with the above-named structures at an early stage of development.

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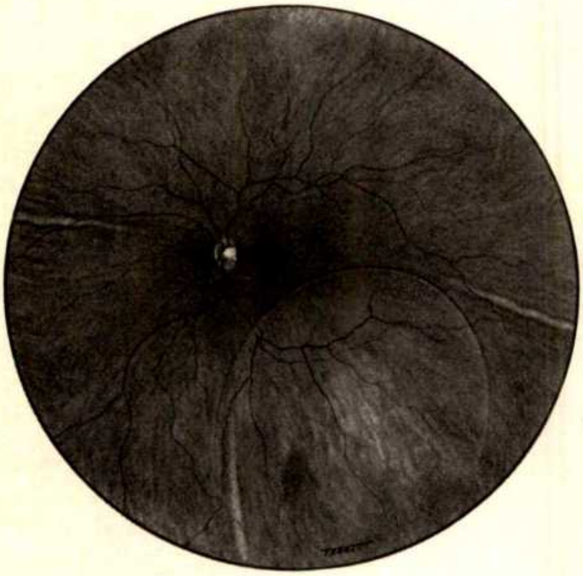

FIGURE *Transparent globular cyst in vitreous of left eye.*

Cysts may arise from the vitreous after the closure of the foetal cleft (Perera, 1936) and they have been described in association with colobomata. In the case reported here no association with developmental remnants could be found.

Cysts may form after liquefaction of the vitreous, as described by Teng and Chi (1957). Here anterior contracture of the vitreous occurs leaving the posterior part liquid; this may be described as a posterior vitreous detachment, the posterior hyaloid membrane becoming detached.

It is possible that this process had occurred in the case described above, and as liquefaction of vitreous is an undoubted factor in the production of retinal detachment, it is possible that this type of cyst is a precursor of retinal detachment.

Summary

A case of fixed vitreous cyst is described, and the possible aetiology of such cysts is briefly described.

My thanks are due to Mr. T. Tarrant of the Institute of Ophthalmology for the fundus painting.

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Correspondence

Corneal vascularization

To the Editorial Committee of the **British Journal of Ophthalmology**

SIRS,—In an article entitled "Corneal vascularization induced experimentally with corneal extracts" (*Brit. J. Ophthal.*, 1969, **53**, 827), P. J. Folca, in a well-designed experiment, suggests that there is no relationship between the degree of corneal swelling and concomitantly produced experimental corneal vascularization. The author concludes that after disorganization of corneal tissue, the release of a vessel-stimulating factor results in corneal neovascularization and that the neovascularization does not appear to be mediated by the production of corneal swelling.

I should like to call Mr. Folca's attention to two articles. In the first, "Congenital hereditary corneal dystrophy" (*Amer. J. Ophthal.*, 1960, **50**, 1114), A. E. Maumenee points out the association of limbal corneal oedema in combination with the absence of stromal vascularization and suggests that the mere presence of oedema in the periphery of the cornea is insufficient to stimulate neovascularization. In the second, "Corneal edema and corneal vascularization" (*Amer. J. Ophthal.*, 1968, **65**, 882), J. L. Baum and E. Martola describe a series of patients with Fuchs's dystrophy in whom there was no corneal vascularization and whose mean limbal corneal thickness was 0·919 ± 0·026 mm. (S.E.M.). The paper also presents a second series of patients with actively vascularized corneae, whose mean limbal corneal thickness was 0·849 ± 0·026 mm. (S.E.M.). The results of the study indicate that a small number of patients are to be found with long-standing limbal oedema and no evidence of vascularization in the oedematous area immediately adjacent to the limbal blood vessels. When adjusted for age group, the limbal corneal thickness in those patients with bullous keratopathy without vascularization was on average approximately 47 per cent. greater than normal, while in the group with active limbal vascularization, the limbal corneal thickness was on average approximately 27 per cent. greater than normal. The authors suggest that corneal oedema is a necessary but not a sufficient stimulus for neovascularization.

In summary, Folca has suggested, on the basis of his experimental results, that corneal oedema is an insufficient stimulus for corneal neovascularization. He has, however, neglected to document the work of previous authors who reached a similar conclusion based on their own data and experimental evidence.

I am in sympathy with the present-day author who must search through a voluminous literature for pertinent articles before presenting his own data. Fortunately, the author is aided in many cases by the reviewer of the journal to which he has submitted his article for publication.

Sincerely yours,
JULES L. BAUM

TUFTS UNIVERSITY SCHOOL OF MEDICINE,
NEW ENGLAND MEDICAL CENTER HOSPITALS,
171 HARRISON AVENUE, BOSTON, MASS., 02111, U.S.A.
March 26, 1970

Book review

The Cornea. Macromolecular Organization of a Connective Tissue [Papers from a Symposium held in Kyoto, Japan, 1967.] Edited by M. E. LANGHAM. 1969. Pp. 239, figs, refs. Johns Hopkins Press, Baltimore and London. (86*s*.)

Dr. Johnson remarked (amongst other things) about Lord Chesterfield's patronage that "had it been early, it had been kind". The present volume contains papers presented at a Symposium at

Kyoto in 1967 and had it appeared sooner its value would have been enhanced; during the last 2 years much water has flowed through corneae.

Within the compass of this review, it is not possible to discuss the individual contributions in detail and the reviewer can do no more than indicate the contents.

The book is divided into three parts: corneal epithelium (5 papers), stroma (7 papers), and endothelium (1 paper). In Part I Zadunaisky discusses the evidence of active transport of chloride in *Rana catesbiana* and Green presents some extremely careful work in support of his theory that the influx of Na^+ across the epithelium plays a primary role in maintaining corneal thickness. Green's notion of "bound sodium" (and especially the second paragraph on p. 64) is less than transcendentally clear and his interpretation may well be questioned. Hedby and Mishima compare the hydraulic conductivities in all three layers of the cornea, and this section is completed by Kikkawa (Intracellular potentials) and Sigiura ("Polygonal" cells). Part II deals mainly with the physical chemistry of the stroma. Mathews describes the connective tissue matrix and Langham, Hart, and Cox discuss the lattice structure of collagen fibrils in relation to the MPS ground substance. (In the proceedings of a symposium held in 1967, it seems a little unfair for Hart to give references dated 1969—and, having aroused the reader's interest, to cite these as "unpublished" or "in press"). Maurice provides a deceptively simple code and raises many interesting points on the availability of corneal water for the distribution of solutes. Part III consists of a single paper by Mishima, Kaye, Takabashi, Kudo, and Trenberth, which gives an excellent account of an alternative to Green's hypothesis: that corneal thickness is regulated primarily by the endothelium. This paper should be read together with Green's contribution and it would have been interesting had the volume concluded with a report of the discussion which must, inevitably, have taken place.

These proceedings are clearly intended rather for serious students of corneal function than for clinicians and one must feel greatly indebted to the Editor for assembling an account of the *status quaestionis* which will be valuable for many years to come.

Notes

International Symposium on Ocular Cryosurgery

Rome, October 17–18, 1970

An international symposium on ocular cryosurgery will be held in Rome, on October 17–18, 1970, by the Italian Ophthalmological Society. The moderator will be Dr. G. B. Bietti.

The speakers will be Dr. J. J. Bellows (*Chicago*), Dr. C. J. Casanovas (*Barcelona*), Dr. A. De Roetth, Jr. (*New York*), Dr. T. Krwawicz (*Lublin, Poland*), Dr. H. Lincoff (*New York*), and Mr. K. Rubinstein (*Birmingham, England*).

Appointed discussers will be Drs. S. P. Amoils (*Johannesburg*), B. Boles Carenini (*Cagliari, Sardinia*), G. Dogo (*Padua*), D. Forlani (*Bologna*), C. Galeazzi (*Milan*), A. Grignolo (*Genoa*), F. Hollwich (*Münster*), P. Moreau (*Dijon*), N. Orzalesi (*Cagliari, Sardinia*), M. R. Pannarale (*Rome*), L. Scullica (*Rome*), and W. Straub (*Marburg*).

Ophthalmologists attending the Symposium and wishing to take part to the discussion should send in the subject of their contribution in advance.

More detailed information may be obtained from J. Pecori-Giraldi, Ph.D., Secretary, Clinica Oculistica dell'Università, Policlinico, 00161 Rome, Italy.

European Contact Lens Society of Ophthalmologists

The European Contact Lens Society of Ophthalmologists is recognized by the International Contact Lens Association of Ophthalmologists. It is hoped to hold yearly meetings, each time in a different country, and also meetings in association with the European Congresses of Ophthalmology.

Ophthalmologists who are interested in becoming members should write to the General Secretary, Dr. Hanfried Laue, 8 Munchen 15, Nussbaumstrasse 14, or to the President, Mr. M. Ruben, Moorfields Eye Hospital, High Holborn, London, W.C.1.

Obituary

Charles Horace Bamford, 1903–1970

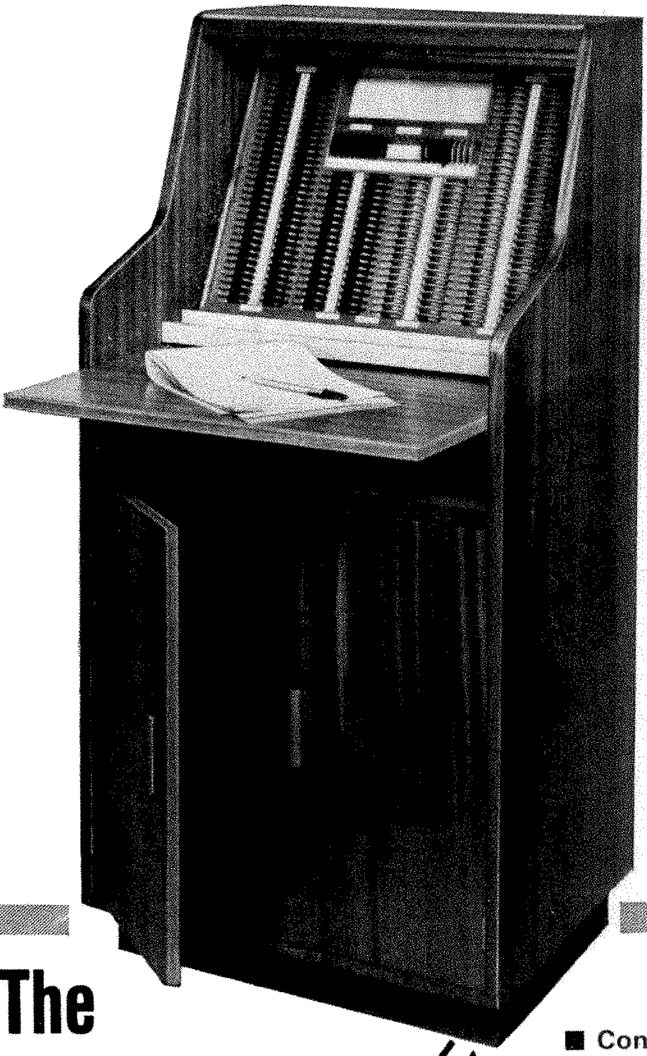
Charles H. Bamford was a much respected and beloved ophthalmologist in Derbyshire. He was educated in Manchester and after serving as a house officer in the Manchester Royal Eye Hospital he went to Derby in 1928 where he spent his professional life in association with the Derbyshire Royal Infirmary. He was responsible for raising the standard of the ophthalmic department of this hospital to its present high level including the early establishment of an orthoptic department. His interest, however, was not limited to his own specialty and he occupied a prominent place in the control of policy in the hospital and, indeed, in the whole of medicine in Derbyshire.

He was an enthusiastic supporter of the Oxford Congress, serving on its council from 1947 to 1970 and occupying the post of vice-president in 1959–60. He was also a president of the Midland Ophthalmological Society and of the Derby Medical Society and was an original member of the British Orthoptic Board. A keen golfer, a prominent Mason, and a member of the Boxing Board of Control, his interests extended far beyond ophthalmology; but his courtesy and humility combined with unusual enthusiasm will be the qualities for which he will be remembered. His wife died in 1968.

Marjorie Perrers Taylor, 1901–1970

Miss M. Perrers Taylor of Thorpe, Summerfield, Cambridge, died on April 4, 1970, at the age of 69, after prolonged ill health which she bore in a manner characteristic of her indomitable spirit. A student of Charing Cross Hospital, she qualified in 1921 and held general and specialized posts in London and Birmingham, obtaining the D.P.H. in 1924 and D.O.M.S. in 1929. In 1931 she started to practise ophthalmology in Cambridge; she was ophthalmic surgeon to Newmarket General and Fulbourn Hospitals, and consultant ophthalmologist to the Isle of Ely County Council and the Cambridge Society for the Blind. From 1946 she carried out research on the effects of radiation on the eye at the Radiotherapeutic Centre, Addenbrooke's Hospital. During the war she deputized as honorary consultant in the Ophthalmic Department, Addenbrooke's Hospital.

She was held in high esteem by her colleagues and patients by reason of her integrity, high standards, and devotion to her work. She had a busy practice, and took great interest in her house and garden which she tended with enthusiasm; she was a keen philatelist. She lived and practised in the City of Cambridge for the greater part of her professional life, moving out to the country when ill health compelled her retirement. She will be greatly missed by her inner circle of relatives and a larger outer circle of colleagues, patients, and friends.



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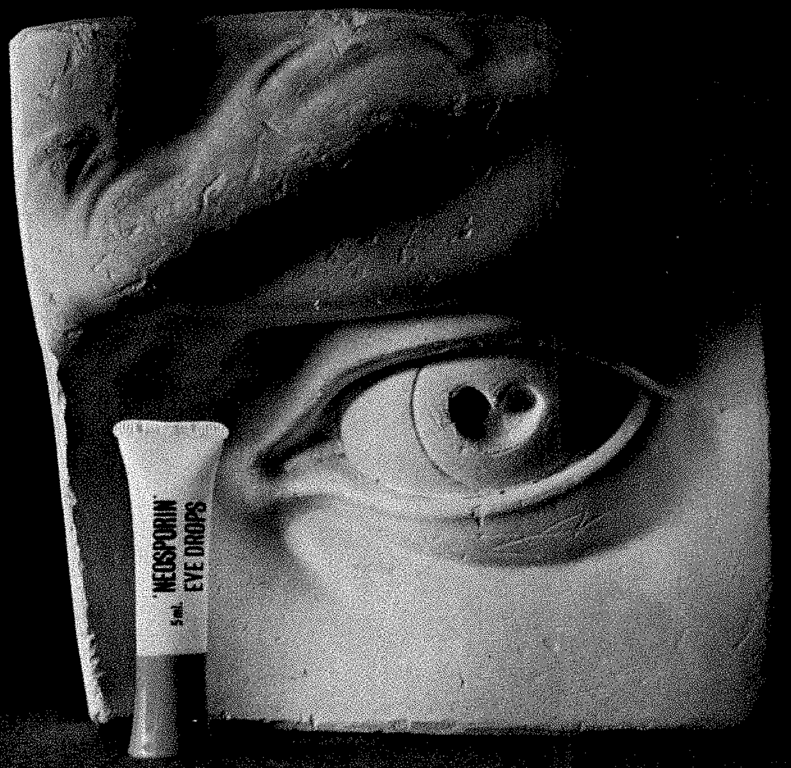

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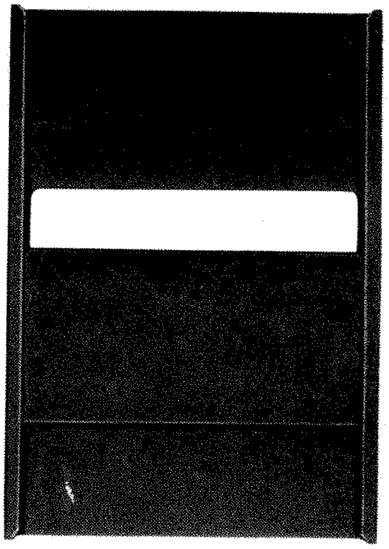

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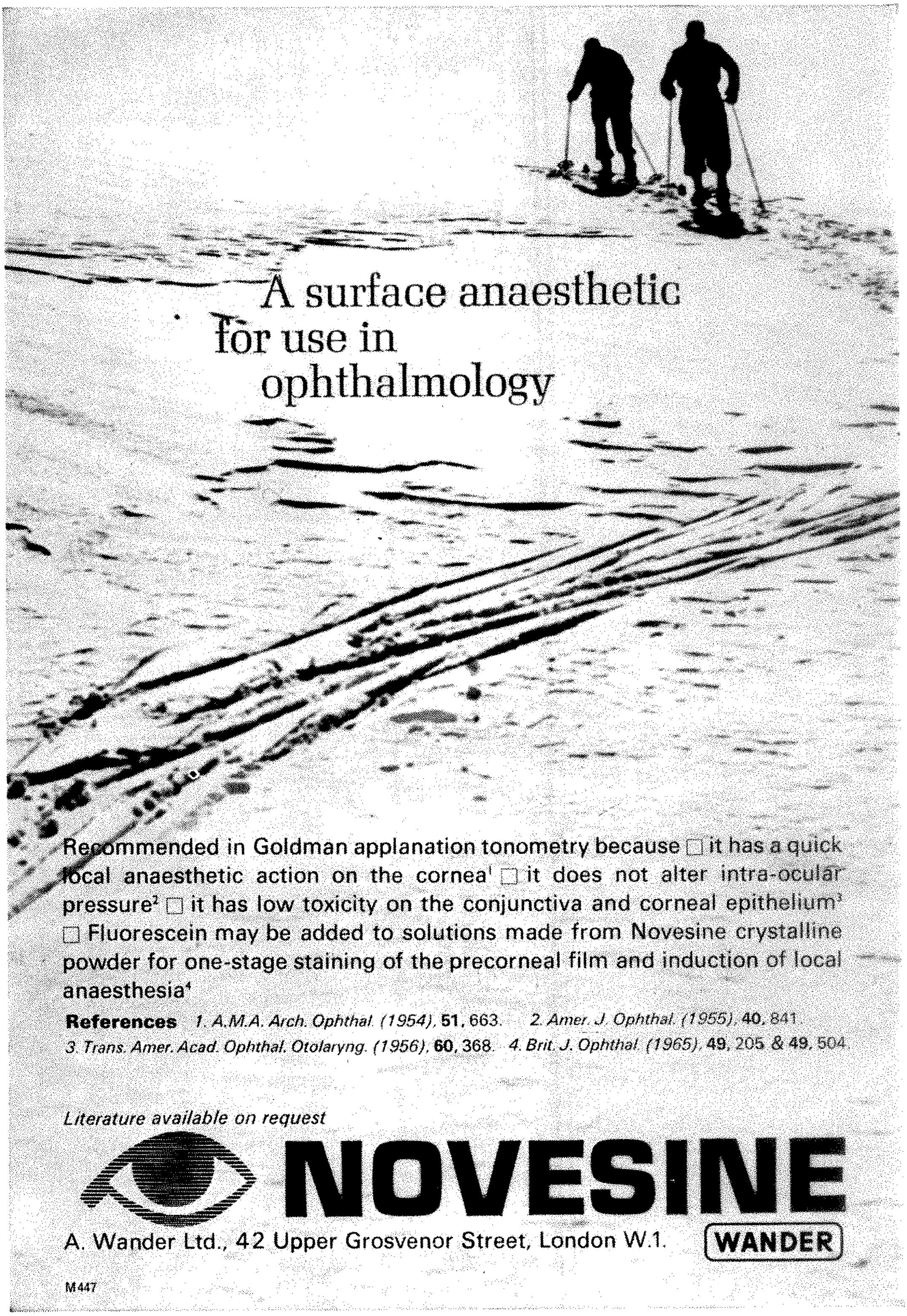

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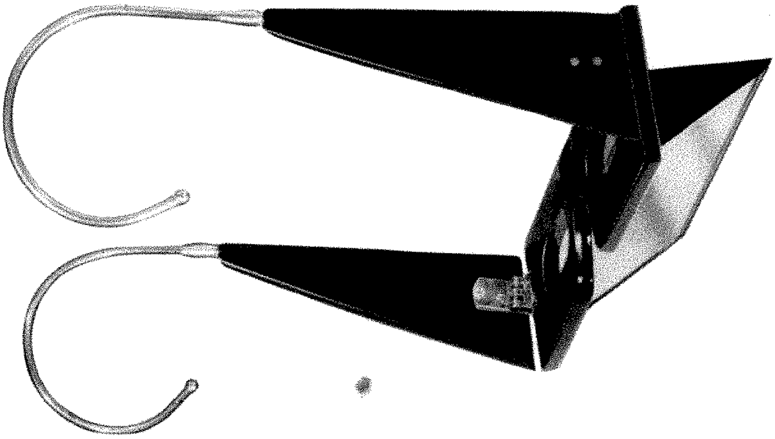

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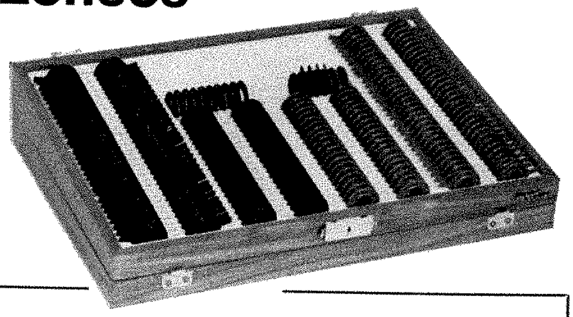

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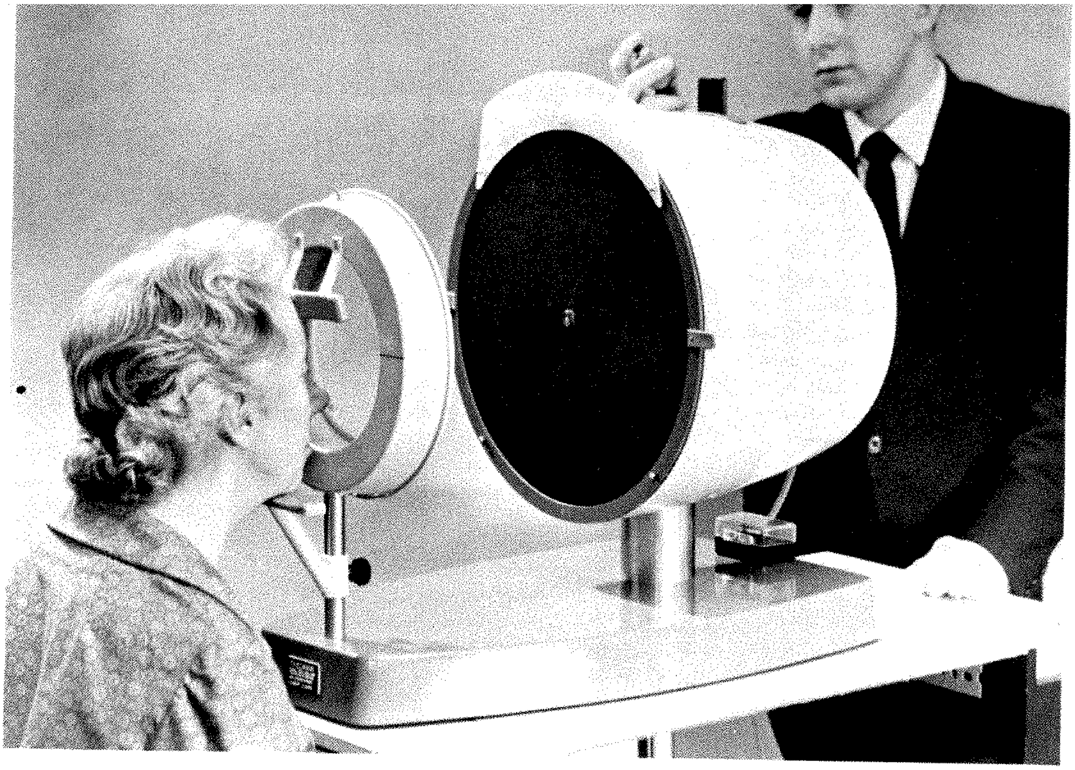

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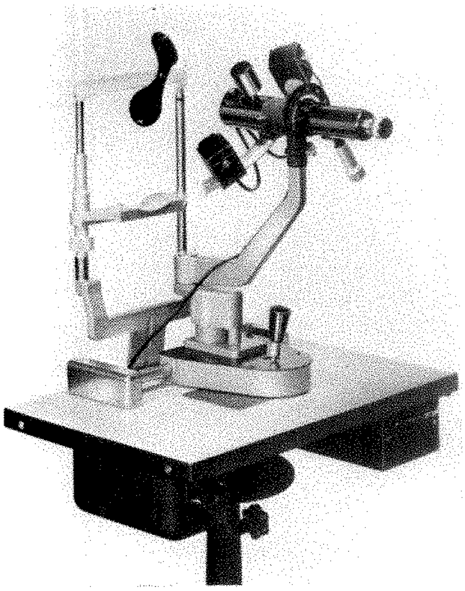

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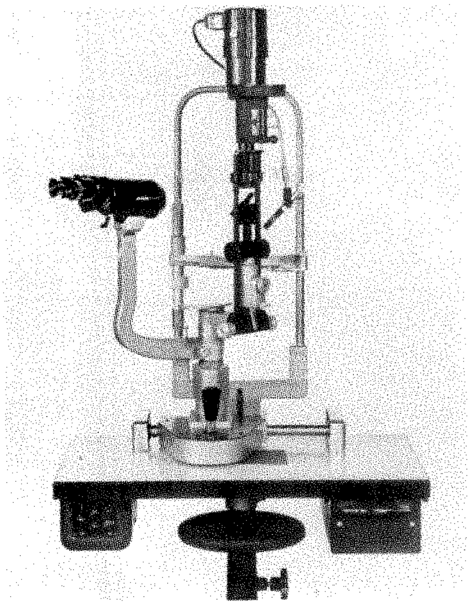

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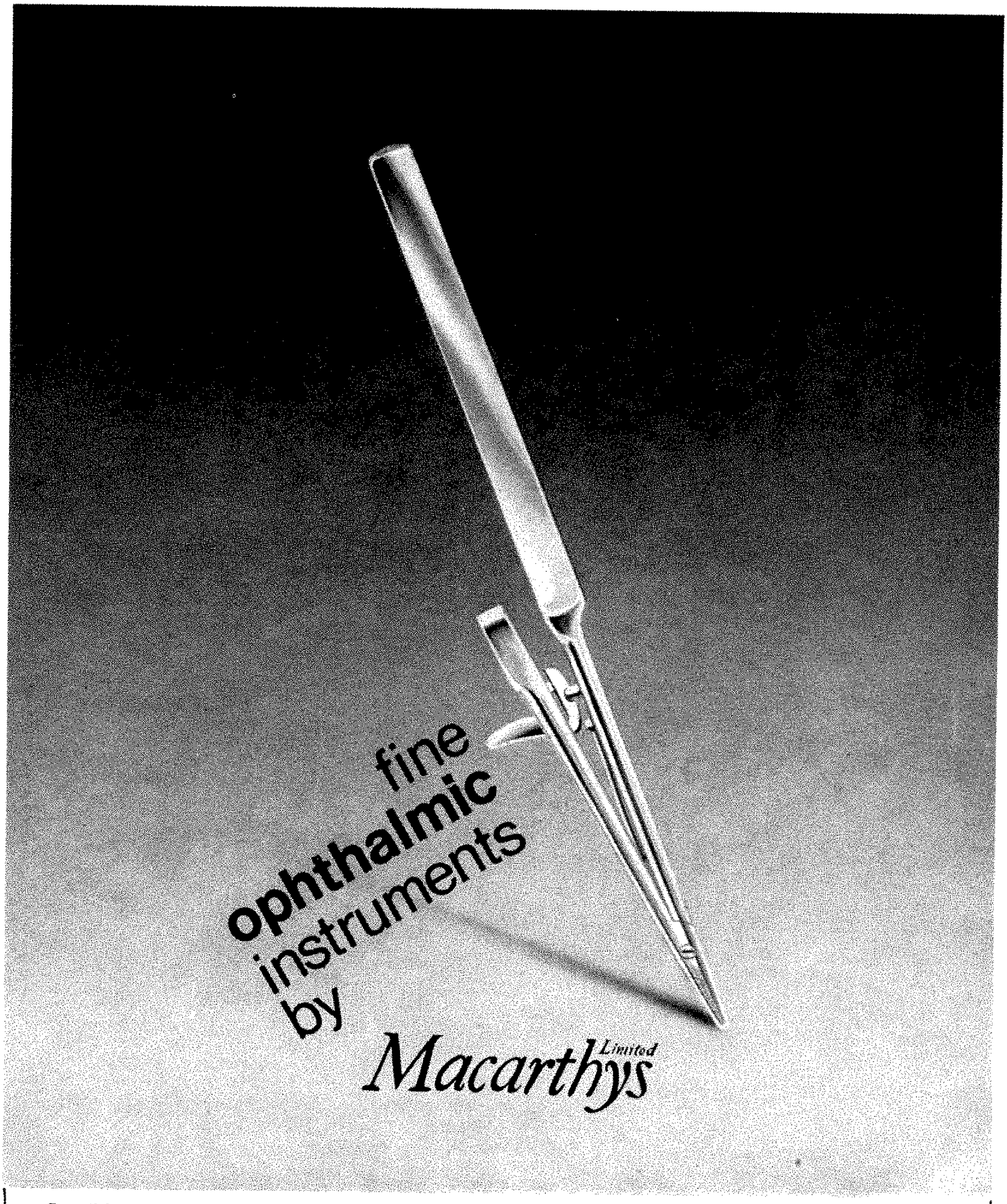

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Communications

Marginal ulceration of the cornea

A. H. CHIGNELL, D. L. EASTY, J. R. CHESTERTON, AND J. THOMSITT

Moorfields Eye Hospital, City Road Branch, London

Marginal ulceration of the cornea represents a common ophthalmic problem. Duke-Elder and Leigh (1965) described two main topographical types: the simple marginal ulcer, and superficial marginal keratitis, the latter being a more extensive lesion which may progress to form a ring ulcer. The simple marginal ulcer is the object of this study (Fig. 1). The onset is heralded by pain and photophobia and the symptoms may closely resemble those of a foreign body. Objectively, one or more infiltrates develop in the superficial corneal stroma and loss of the overlying corneal epithelium then leads to the formation of a characteristic grey ulcer, situated in the marginal zone of the cornea and separated from the limbus by a clear corneal zone. There is an associated conjunctival reaction with hyperaemia and chemosis. The lesions usually run a course of about

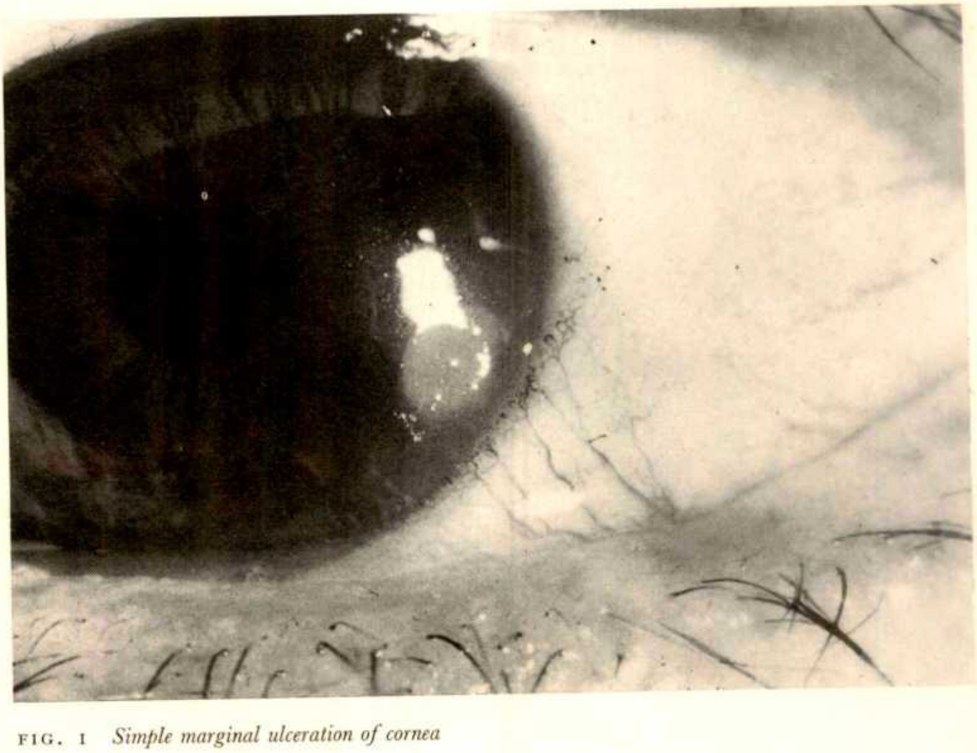

FIG. 1 *Simple marginal ulceration of cornea*

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one week, and then resolve leaving a small scar. The symptoms are commonly of sufficient severity to result in loss of time from work.

The aetiology of the condition remains rather obscure, but the strong association between the marginal ulcer and the presence of pathogenic staphylococci in the conjunctival sac and lid margins led Thygeson (1946) to believe that they resulted either from a toxic product of the staphylococcus or from a sensitivity response to its presence. Thygeson (1969) again drew attention to the association between marginal ulceration and long-standing staphylococcal blepharitis. Various methods of treatment have been advocated, *e.g.* carbolization, antibiotic drops, and corticosteroid drops. As yet no definitive trial of treatment has been recorded. The purpose of this study was to collect data relevant to aetiology in patients with marginal ulceration and to institute a therapeutic trial.

Method

The study was carried out on 84 patients attending Moorfields Eye Hospital, City Road, over a period of one year. Patients with direct involvement of the cornea from conjunctival disease (*e.g.* trachoma, rosacea) were excluded. Any patient who had already received any treatment for the present attack was not considered for the trial.

A careful history was taken from each patient, and details of age, occupation, symptoms, associated general disease, previous attacks, and precipitating factors were recorded at the initial interview. A careful examination was made of the ocular adnexa; details of lid, conjunctival, and corneal diseases were noted. The lesion itself was assessed both unstained and stained with fluorescein and its size was measured by a calibrated slit beam on a Haag Streit 900 slit lamp. Patients were seen every other day and considered to be cured when the symptoms had resolved and the corneal epithelium had healed, as shown by staining with fluorescein.

Investigations

Cultures were taken from the lid margins of both eyes, rubbing a dry cotton-tipped applicator along the lid margins and inoculating blood agar plates.

Conjunctival cultures from both inferior fornices were taken with a platinum wire loop. Scrapings and cultures were obtained from those patients who were to be treated by carbolization by scraping the lesion with a platinum spatula after the instillation of anaesthetic drops (amethocaine). The culture was made by inoculation of blood agar plates. Scrapings were placed on a glass slide and the dry preparation was stained with Giemsa and examined by light microscopy. In each case, the haemoglobin was estimated together with the erythrocyte sedimentation rate (ESR), and a full blood count was performed.

Therapy

The patients were divided into two main groups: the first 23 patients in the study were treated by carbolization and a second group of 61 underwent a double-blind therapeutic trial conducted on a randomized coded basis. This division was necessary because it was not possible for observers to be unaware of treatment given to the carbolization group.

CONTROLS

A third group of 100 patients examined at a later date had no evidence of external ocular disease. Cultures were taken from the lids and conjunctival sacs between the months of August and December to provide a group for comparison purposes.

GROUP I (23 cases)

The ulcer was lightly carbolized under local anaesthesia; after this gutt. hyoscine 0·5 per cent. were instilled and a pad and bandage were applied for 48 hours.

GROUP 2 (61 cases)

In the double-blind coded series, "trial drops" only were prescribed; each patient used one of the following:

(*a*) Gutt. Predsol 0·25 per cent. (preserved in 0·004 per cent. phenylmercuric nitrate)
(*b*) Gutt. Neomycin 0·5 per cent. (preserved in 0·004 per cent. phenylmercuric nitrate)
(*c*) Control drops (0·004 per cent. phenylmercuric nitrate).

The allocation of drops was determined by the pharmacist by the use of random tables. In this group, no mydriatics were instilled and the eye was not bandaged, and the drops were instilled 2-hourly by day only.

The patients were seen every 2 days, and were removed from the trial if the condition was seen to be worsening or there had been no improvement in the ulcer by the end of 5 days; in accordance with standard practice in conducting a double-blind trial, neither the observers nor the patients knew the type of medication being administered.

Results (84 cases)

AGE

The age range was 18 to 75 years;

66 per cent. were between 40 and 60 years old,
18 per cent. were less than 40 years old,
16 per cent. were more than 60 years old.

SEX

The male : female ratio was 3·5 : 1.

PREVIOUS ATTACKS

39 per cent. of the patients had had at least one authenticated previous attack; an additional 20 per cent. thought they had suffered a previous attack which was not verified.

PRECIPITATING FACTOR

10 per cent. of the total gave a history of a foreign body which had entered the eye, usually a day or two before the onset of the attack. We found no case where a foreign body was actually present with a manifest marginal ulcer. A further 11 per cent. gave a vague history of a foreign body being the precipitating factor.

EYE AFFECTED

In 46 cases (56 per cent.) the right eye was affected, and in 38 cases (44 per cent.) the left eye.

DISTRIBUTION

The ocular distribution of the ulcers bore no obvious relationship mechanically to any associated lesion of the lid (*e.g.* a chalazion). The distribution is summarized in Table I (overleaf).

MORPHOLOGICAL APPEARANCES

These were characterized by the formation of single or multiple infiltrates which subsequently coalesced, and the breaking down of the overlying corneal epithelium resulted in the formation of a typical ulcer. In all our cases this ulcer was separated from the limbus by a clear area of cornea although the bloodvessels at the limbus became dilated. It was found that the character of the ulcer did not vary according to the corneal site.

Table I *Corneal distribution of marginal ulcers in 84 patients, showing quadrant involved*

Eye		*Right* (46)		*Left* (38)	
		Temporal	*Nasal*	*Temporal*	*Nasal*
Quadrant	Upper	12	12	10	6
	Lower	8	14	14	8

SEASONAL INCIDENCE

There did not appear to be any marked seasonal incidence; 47 cases occurred between October and March, and 37 between May and September.

GENERAL HEALTH

21 patients had recently suffered or were currently suffering from an upper respiratory tract infection.

HAEMATOLOGY

Two patients were found to be suffering from mild iron deficiency anaemia. Three had a slightly raised ESR. These three patients were chronic bronchitics. All other haematological findings were within normal limits.

LIDS

Ten patients were considered to be suffering from infective blepharitis. A further twenty had mild squamous blepharitis. A further seven had active styes or inflamed meibomian glands.

In all the results recorded above, there was even distribution of all factors in each of the treatment groups.

CONJUNCTIVAL CULTURES

The results obtained from the whole series of 84 cases of marginal ulceration are summarized in Table II. There were 24 patients (29 per cent.) from whom *Staphylococcus aureus* was isolated. In twelve of these the organism was isolated from one site only, in six from two sites, in three from three sites, and in four from four sites.

Table II *Distribution of organisms in 84 cases of marginal ulceration*
Figures in brackets in columns represent percentage of total: some showed more than one organism

Organism (*no. of cases*)			Staph. aureus (24)	Staph. albus (44)	Morax-ella (4)	B. xerosis (22)	*Miscellaneous* (2)
Site	Conjunctiva	Right	9 (11)	22 (25)	2 (2)	12 (14)	0
		Left	9 (11)	21 (25)	3 (3)	12 (14)	*N. catarrhalis* (1) α-haemolytic streptococci (1)
	Upper and lower lids	Right	11 (12)	32 (38)	0	12 (14)	0
		Left	15 (16)	36 (43)	0	14 (17)	0

Table III (opposite) shows the relationship of *Staph. aureus* organisms to the side of the lesion. There was a greater tendency for the *Staph. aureus* to be obtained from either the lids or conjunctival sac on the same side as the eye affected by a marginal ulcer.

Table III *Relationship between eye affected by marginal ulceration and side from which* Staph. aureus *was isolated in* 24 *cases*

Side from which Staph. aureus *was isolated*	*Eye affected*	
	Right	*Left*
Right upper and lower lids and conjunctival sac	9	2
Left upper and lower lids and conjunctival sac	3	10

Table IV summarizes the findings from the control group of 100 patients who had no evidence of external ocular disease. In 11 per cent. *Staph. aureus* was isolated, compared to 29 per cent. of the cases of marginal ulceration.

Table IV *Percentage bacteriological distribution in* 100 *subjects with no evidence of external ocular disease (numbers of patients in brackets: some showed more than one organism and others showed none)*

Organism (no. of cases)			Staph. aureus (11)	Staph. albus (67)	Moraxella (4)	B. xerosis (11)	*Miscellaneous* (4)
Site	Conjunctiva	Right	0	10	2	6	*N. catarrhalis* (1)
		Left	4	15	0	7	Koch-Weeks bacillus (1) *E. coli* (1) Pneumococcus (1)
	Upper and lower lids	Right	7	55	1	7	0
		Left	8	46	1	4	0

LID CULTURES

The results are given in Table II.

CONJUNCTIVAL SCRAPINGS

In nearly all cases the results were not informative and gave no clue to the aetiology. No inclusion bodies were found and the cytology did not suggest any viral disease. Scrapings consisted mainly of epithelial cells and a few polymorphs and mononuclear cells.

SCRAPINGS FROM MARGINAL ULCERS

Material was difficult to obtain and showed only degenerate epithelial cells in most cases. There was a striking absence of cellular infiltration. No organisms were seen.

CULTURES FROM MARGINAL ULCERS

No growth was obtained from any of the 23 cases cultured.

Results of Therapy

(Table V and Figs 2, 3, 4, and 5, overleaf)

The successes and failures at the fifth day of the trial in the Predsol group were compared with the successes and failures in the control group by the χ^2 test. It was found that there was a significant difference, the Predsol treatment being distinctly the more effective (P <

Table V *Number of patients successfully treated in each group by the fifth day of the therapeutic trial (percentages in brackets)*

Therapy	*Total in each group*	*Resolution*		*Trial failures*	*Significance compared with controls*
		At fifth day	*After fifth day*		
Carbolization	23	12 (52)	10 (43)	1 (5)	P > 0·05
Control	19	8 (42)	8 (42)	3 (16)	
Neomycin	19	6 (32)	7 (36)	6 (32)	P > 0·05
Predsol	23	21 (91)	2 (9)	0	P < 0·001

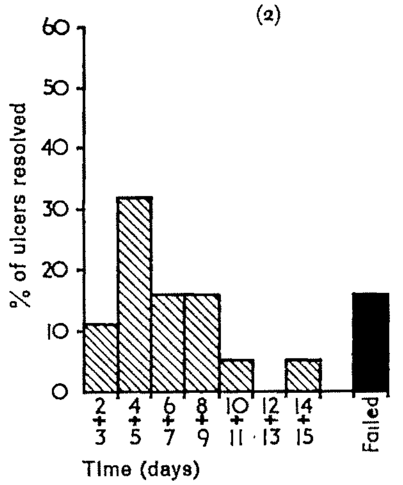

FIG. 2 *Histogram demonstrating rate of resolution in nineteen patients treated with "control" drops*

Each block represents the number of patients cured during 2 days

F = number of patients who eventually failed to respond or were becoming worse on the fifth day

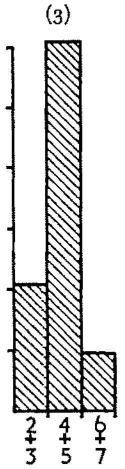

FIG. 3 *Rate of resolution in 23 patients treated with Predsol drops*

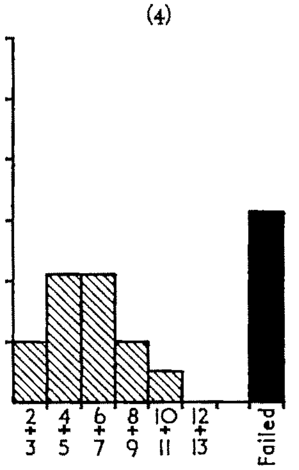

FIG. 4 *Rate of resolution in nineteen patients treated with Neomycin drops*

F = number of patients who failed to respond and were removed from the trial

0·001). A further comparison between the control and Neomycin groups ($\chi^2 = 0·4$) and between the control and carbolization groups ($\chi^2 = 0·73$) showed no significant difference. These findings indicate that, of the eyedrops used, only corticosteroid drops proved to be of benefit in the treatment of this condition.

Discussion

The aetiology and therapy of marginal ulcers have not been frequently investigated. Thygeson (1946) examined a series of patients and suggested that these ulcers are either toxic or hypersensitive in nature.

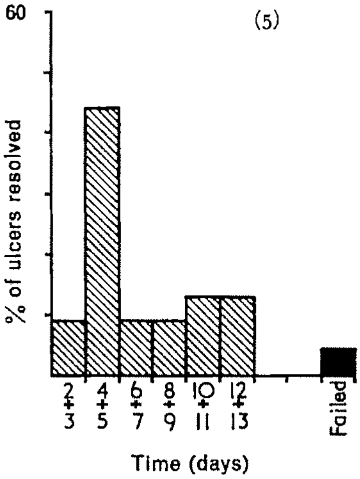

FIG. 5 *Rate of resolution in* 23 *patients treated with carbolization*

F = number of patients who failed to respond and were removed from the trial

A high percentage of our cases occurred in patients between the ages of 40 and 60 years and it is interesting to note that no case was found in children or in very old persons. The fact that males were affected to a greater extent than females might suggest a traumatic factor in the aetiology, but the question of trauma was difficult to estimate. The symptoms of the two conditions are remarkably alike, but no foreign body was found in the presence of a marginal ulcer.

There was a considerable tendency for the lesions to recur, as is well known (39 per cent. in our series). It was considered possible that local staphylococci may provide a source of further attacks of marginal ulceration; that is, the marginal ulcer may represent a hypersensitivity or toxic response.

21 patients (25 per cent.) had recently suffered or were currently suffering from an upper respiratory tract infection. Pathogenic staphylococci were isolated from 11 per cent. of the control group, as compared to 29 per cent. of those with marginal ulceration. These bacteriological observations appear to confirm Thygeson's observations (he found pathogenic organisms in all but sixteen of his 133 cases), and it seems reasonable to assume that local pathogenic staphylococci play some part in the aetiology. A difference between the method of collection of lid margin and conjunctival cultures might account for the discrepancy in the two series. We also found that the pathogenic staphylococci are more likely to be found on the same side as the ulcer, either on the eyelids or in the conjunctival sac.

The fact that no organisms could be isolated from the lesions themselves would indicate that they are not caused by direct infection, and this is substantiated by the absence of a cellular response in the scrapings from the lesions.

In the therapeutic trial it was found that corticosteroid drops were the treatment of choice. The success of this therapy would support the theory that the lesion is a sterile inflammation, the aetiology of which is obscure. It is clear that the prompt healing induced by the administration of corticosteroid drops results in considerable economic benefit because it permits the early return to work of the patient. Vaughan (1958) mentioned that steroids may be used in treatment.

The failure of the group receiving Neomycin drops to respond also supports the belief that these lesions are not due to infection of the cornea.

In the group of patients treated by carbolization it was necessary to instill a mydriatic and keep the eye bandaged for 2 days to prevent discomfort, and this usually resulted in a loss of working days. This method has no advantage over non-surgical treatment and its use should therefore be discontinued. It should be noted that no attempt was made to suppress or eradicate the growth of pathogenic staphylococci in the lid margins by any medication. The possible effect of such treatment on the course of the corneal lesion or on the prevention of recurrences could well form the subject of a further study.

Summary and Conclusions

(1) An investigation is reported of the aetiology and treatment of simple marginal ulceration of the cornea in 84 patients.

(2) From the results of morphological and bacteriological studies no definite conclusions can be drawn concerning the aetiology. It is clear that *Staphylococcus aureus* plays some part in the production of a marginal ulcer (29 per cent. of cases in our study), but this organism is by no means invariably present. The mechanism by which the organism produces a marginal ulcer is obscure, although the success of corticosteroid drops and the findings in the scrapings and cultures from the ulcers would support the theory that the ulcers might represent a hypersensitivity or toxic response to pathogenic staphylococci.

(3) In comparing the effects of carbolization, corticosteroids, or antibiotic drops with the results in controls, it was found that corticosteroid drops were highly effective in shortening the course of the ulceration, whilst both carbolization and antibiotic drops showed no significant difference from the control group. We feel that carbolization should be discontinued as a method of treatment.

(4) Early administration of steroid drops clearly results in a more rapid resolution of symptoms and signs compared with other forms of treatment with consequent economic advantages in early return to work by the patient.

We are grateful to Prof. Barrie Jones and Mr. N. S. C. Rice for their help and encouragement in this project, to Prof. Norman Ashton and his department at the Institute of Ophthalmology for their assistance in the investigations performed on the patients studied in the survey, and to the Department of Audio-Visual Communication of the Institute of Ophthalmology for preparing the histograms.

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Autoimmunity and the retina

1. Antigenic specificity of photoreceptor cells

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The first suggestion that the retina might be antigenic was made by Hess and Römer (1906). This was later confirmed by Burke, Sullivan, Petersen, and Weed (1944), who demonstrated changes in the retina and pigment epithelium after injecting adult lens antiserum into chick embryo. Maisel and Langman (1961) studied the distribution of lenticular antigens in various tissues of the chick eye and described at length how the cornea, uvea, and pigment epithelium of the retina share some antigens in common with the lens. The uveitogenic nature of the retina was first suspected by Wacker and Lipton (1965) in guinea-pigs, and was later confirmed in rabbits (Wacker and Lipton, 1968; Aronson, 1968) and rhesus monkeys (Lerner, Stone, Meyers, and von Sallmann, 1968; von Sallmann, Meyrs, Stone, and Lerner, 1969). The precise antigenic locus (or loci) in the retina, however, is as yet undefined, in part because "fractionation of retinal tissue to approach isolation of an antigenic agent has not been attempted" (von Sallmann and others, 1969).

This present study, therefore, was designed to investigate the antigenic properties of the outer limbs of the photoreceptor cell, as it is these which are most commonly affected in retinal dystrophies of doubtful aetiology.

Material and methods

IMMUNIZATION

Dissected retinae from fresh bovine eyes were homogenized in cold saline, distributed in 0·2 ml. aliquots, and stored at −30°C. Each retina (wet weight 600 mg.) yielded 1 ml. tissue extract.

The animals were healthy rats and rabbits, free from any eye disease. Each experimental animal was given a subcutaneous dose of the extract (reconstituted to 1 ml. in saline) emulsified in Freund's complete adjuvant ($H_{37}Ra$: Difco) injected into the back once a week for 6 weeks. Control animals were given only the adjuvant. One week after the final injection the animals were aseptically bled and the sera obtained were inactivated, adsorbed, and finally stored at −30°C.

PREPARATION OF TEST ANTIGEN

Outer limb suspensions of photoreceptor cells were prepared according to the method of Saito (1938). The modified technique of Collins, Love, and Morton (1952), although better for biochemical studies, is time-consuming and was therefore not considered necessary for the present investigation. The dissected retina was suspended in three times its weight of freshly prepared 45 per cent. sucrose in McIlvaine's citrate-phosphate buffer (pH 7) and shaken for 30 to 45 sec. until greasy. It was then centrifuged at 2,000 r.p.m. for 15 min. The outer limbs separated out in the supernate were recovered after discarding the sediment and recentrifuging the supernate (mixed with four times its volume of the buffer) at 3,000 r.p.m. for 30 min. The sediment was re-suspended in cold saline, homogenized, and then stored in sterile vials at −30°C. for future use as antigen for agar diffusion and haemagglutination tests.

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THE TEST

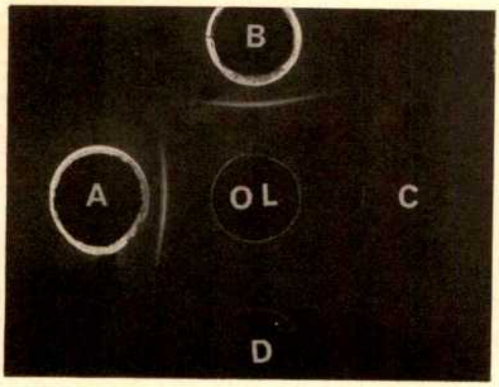
Antibodies against whole retinal extracts and photoreceptor cells were tested by tanned red cell agglutination and two-dimensional double-diffusion tests. Agar plates were prepared with 1·5 per cent. Noble agar in barbitone buffer (pH 8·2; I = 0·075) containing 0·1 per cent. sodium azide. Diffusion was allowed to occur at 4°C. Immunoelectrophoresis of rabbit antiserum was carried out on similar agar plates against antirabbit IgG.

Results

(*i*) Sensitized tanned red cells showed agglutination with test sera from immunized rabbits and rats. There was no agglutination with buffer alone or with non-immune serum obtained from animals receiving only the adjuvant. Furthermore, no agglutination was observed with non-sensitized tanned red cells in immune sera.

(*ii*) On the second day precipitation lines (single with photoreceptor cells and double with whole retinal extracts) were observed by naked eye in the agar plate, and these became heaviest (and showed a reaction of identity) on the fourth day (Figs 1 and 2).

(1)



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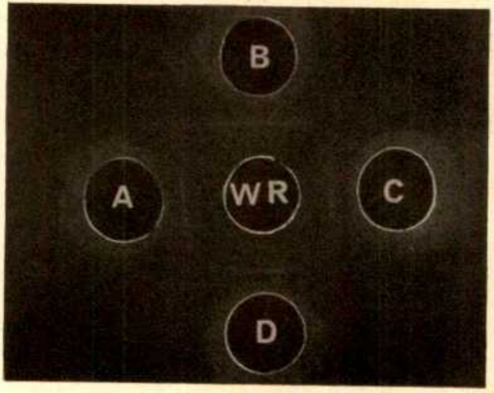

FIG. 1 *Double diffusion gel precipitation: Antisera (A) rabbit and (B) rat demonstrate a single precipitin band against bovine photoreceptor outer limbs (OL). Sera from normal rats (C) and rabbits (D) show no precipitin line.*

FIG. 2 *Agar diffusion precipitin reaction: Antisera (A and B) rabbit and (C and D) rat demonstrate closely placed double bands against whole bovine retinal extract (WR).*

No precipitation was observed with non-immune sera. Occasional faint secondary (Liesegang) lines were seen after long incubation in some of the sectors of the agar plate, but these were probably artefacts produced by environmental changes. Homogenates from rat and bovine retinae cross-reacted and showed a reaction of partial identity (Fig. 3).

(*iii*) Sera from immunized rabbits showed a high level of IgG (Fig. 4).

Comments

The experiment was designed as a prelude to further investigations into the role of antigenic determinants of photoreceptor cells in the pathogenesis of retinal degenerations. Wacker and Lipton (1968), working with whole retinal extracts, suggested the presence of two antigenic substances, one soluble and the other particulate, responsible for immune

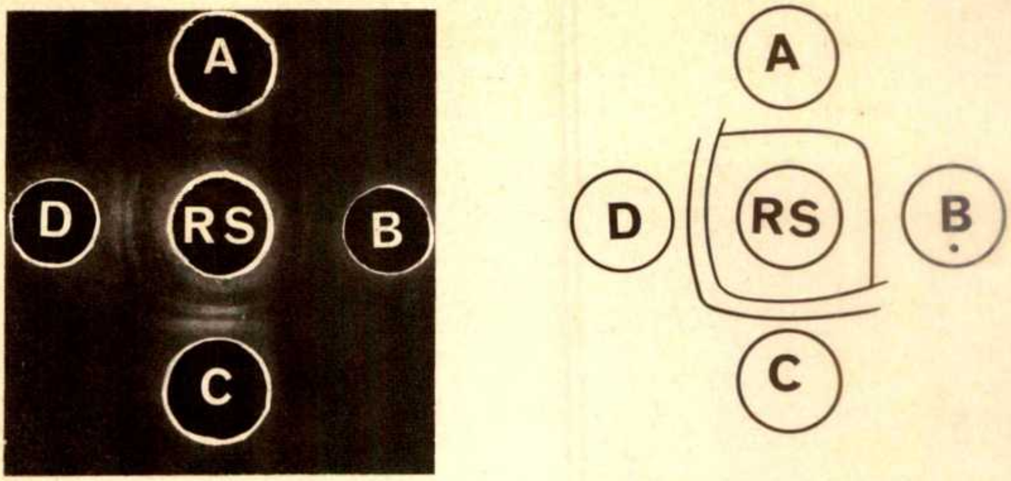

FIG. 3 *Reaction of partial identity between rat (A and B) and bovine (C and D) retinae. (RS) indicates rabbit antiserum against bovine retina.*

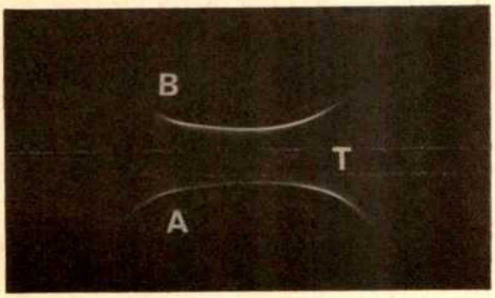

FIG. 4 *Immunoelectrophoresis: Holes (A and B) contain sera from immunized and normal rabbits respectively. Trough (T) contains monospecfic serum against rabbit IgG. Comparatively large precipitin line near (A) indicates high level of IgG in immunized rabbit.*

reactions in guinea-pigs. Aronson (1968) prepared his antigen from whole retinal extract after dialysis and centrifugation and suggested that antigenic substance was present in the supernate. Whether there is one or more than one antigenic substance in the retina—a complex cellular structure functionally and anatomically—is a matter for thorough investigation. It seems certain, however, that one of the antigenic substances is located in the outer limbs of the photoreceptor cells. This assumption is further supported by the fact that some of the immunized animals (Wacker and Lipton, 1965, 1968; Aronson, 1968; Lerner and others, 1968) showed necrosis and degeneration of the outer layers of the retina. Although it has been suggested that these changes were secondary to choroiditis, it is difficult to exclude an antigen-antibody reaction in the retina, especially when retinal immune reactions, quite independent of choroiditis, have been demonstrated in rhesus monkeys (von Sallmann and others, 1969). Yamamoto and Yamori (1966) could not demonstrate with certainty antibodies against bovine opsin extracted with digitonin in rabbit immune sera, but they were of the opinion that the results obtained could be improved if saponin extracts were used, since digitonin extracts are unsuitable for antigen-antibody reactions.

Conclusions

The antigenicity of the outer limbs of the photoreceptor cells has been investigated in rabbits and rats. Specific antibodies have been demonstrated by haemagglutination and precipitation techniques. It is suggested that the role of antivisual cell antibodies in the pathogenesis of retinal dystrophies should make an interesting and possibly a valuable study.

It is a pleasure to record the advice and encouragement given by Prof. Norman Ashton, whose original ideas formed the basis of this investigation. My thanks are also due to Miss E. Robins and Mrs. P. Rawlings for their technical assistance, and to Miss E. FitzGerald for secretarial help.

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Intraorbital amyloid

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Several reviews of ocular amyloidosis have emphasized its origins in the conjunctiva and lid (Halasa, 1965; Stansbury, 1965; Smith and Zimmerman, 1966). The occurrence of orbital amyloid has been considered extremely rare, its pathogenesis speculative, and its place in the spectrum of diseases associated with amyloid deposition uncertain (Groniowski, Bernardczykowa, and Norn, 1965; Howard, 1966; Kassman and Sundmark, 1967). For this reason it is felt that further attention should be called to this entity.

Case report

A 55-year-old Negro male labourer first sought treatment at The Mount Sinai Hospital in February, 1964, because of his concern over the appearance of his left eye. He had noted the onset of protrusion of the eye 10 years earlier, without pain, visual loss, diplopia, or other ocular symptoms. There was said to have been an exposure of both eyes to lime.

The records of another hospital indicated that he had been seen 4 years after the onset and found to have a visual acuity of 20/20 in each eye, marked proptosis of the left eye with fixation of the globe, and a hard mass between the globe and the superior orbital margin. The remainder of the eye examination was recorded as being not remarkable. The general history was negative for systemic illnesses; and the physical examination was non-contributory. CBC, urine analysis, erythrocyte sedimentation rate, and albumin/globulin ratio were normal, as were radiographs of the chest, skull, paranasal sinuses, and optic foramina. The larynx and sinuses were normal on otolaryngological evaluation. A biopsy specimen of the mass was described as "having the consistency of cartilage", and showed histologically "eosinophilic strands of myxomatous material with no definite arrangement, no prominent vessels, and poor in cellular content." The diagnosis was "benign mesenchymal tumour of unknown type, most likely chondroma". Orbital exploration was performed, at which time the tumour could be seen extending to the posterior part of the orbit and into the lid structures. Only incomplete removal was possible.

The patient was seen at a second hospital in July, 1963, 9 years after the onset. Leucopenia, mild albuminuria, and a slightly elevated blood sugar level were found. Lobulated masses were palpated in the region of the previously excised mass, which on biopsy and histological examination were seen to consist almost entirely of amyloid.

At the time of his admission to Mount Sinai Hospital in 1964, examination of the left eye and orbit revealed findings similar to those already described (Figs 1 and 2, overleaf). In addition, the opposite lid contained a firm, localized, non-tender mass supero-nasally, also palpable into the right orbit. The patient was aware of its presence but was uncertain as to its date of onset. Visual acuity could be corrected to 20/20 in the right eye and 20/70 in the left. The central and peripheral visual fields were full in the right eye with a normal blind spot; the field of the left eye showed a superior constriction to 10° (possibly an artefact due to unretractable prolapsed conjunctiva, which was adherent to the upper part of the cornea), and a markedly enlarged blind spot. Intraocular pressure by applanation was 21 mm. Hg in the right eye and 13 mm. Hg in the left. Exophthalmometry readings indicated 4 mm. of proptosis of the left eye. The general physical findings were again unremarkable except for obesity; no thyromegaly, congestive heart failure, or abdominal organ enlargement were found. Albuminuria, hyperglycaemia, and mild leucopenia were present. Other renal function tests were normal, as was liver function, except for an inverted albumin/globulin ratio.

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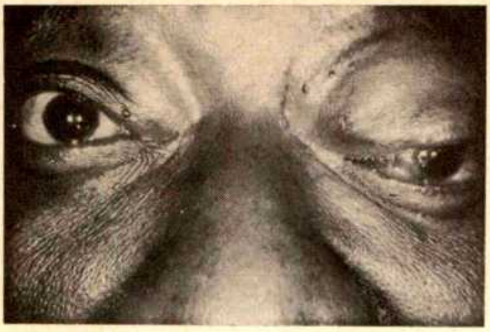

FIG. 1 *Proptosis of left eye. Note fullness above medial canthus of right eye*

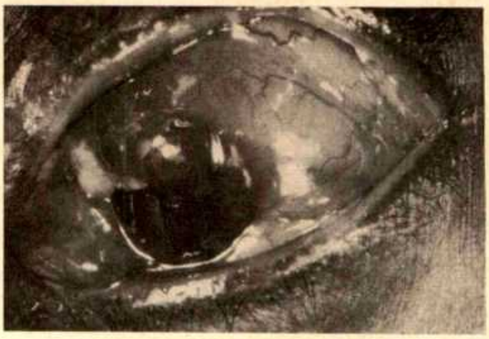

FIG. 2 *Amyloid-infiltrated conjunctiva, left eye*

Protein-bound iodine was normal. The erythrocyte sedimentation rate was significantly elevated. A trace of Bence Jones protein was detected in the urine. Electrophoresis of serum showed diffuse elevation of the gamma-globulin fraction with other components normal. Urine electrophoresis showed a preponderance of protein in the albumin position. Serum macroglobulins, cryoglobulins, and the Coombs and latex-fixation tests were negative. A Congo red test was not done because of the possible dangers associated with this procedure in the dosage appropriate for this patient's size. Radiographs of the chest, sinuses, skull, orbits, and long bones were non-contributory; an electrocardiogram indicated non-specific T-wave changes and normal rhythm with occasional atrial extrasystoles. Sternal marrow showed slight prominence of plasma cells, which appeared normal. Skin tests for tuberculosis, histoplasmosis, coccidioidomycosis, and blastomycosis were negative. Medical and haematological consultants could find no evidence of systemic amyloidosis. Neurological examination revealed absent ankle jerks and a history of occasional numbness and tingling of the extremities. Detailed sensory testing gave normal results. The patient refused rectal, gingival, renal, and liver biopsies.

On February 26, 1964, a limited exploration of the left orbit was performed (the patient at all times refused surgical intervention in the right orbit). Firm, gelatinous material was seen diffusely infiltrating the orbit and upper lid (Fig. 3). Removal of the mass was not possible. A large biopsy was taken, which again proved to be amyloid (Fig. 4), as did a conjunctival biopsy (Fig. 5). Immunofluorescence studies on the specimen indicated 7S gamma globulin in bloodvessel walls. A portion of the specimen was cultured and was negative for fungi and acid-fast bacilli. Postoperatively there was no improvement. The patient has become lost to follow-up, and further search for an underlying systemic disease has not been possible.

Discussion

Amyloidosis is a condition characterized by extracellular deposition in tissues of a substance with certain special staining characteristics. It was once considered a degenerative process involving the deposition of carbohydrates, but is now felt to be a disturbance of protein synthesis, more specifically an infiltration of glycoproteins of variable composition, produced by plasmacytic cells of the reticuloendothelial system (Teilum, 1957). By histochemical techniques it has been shown that there are structural and antigenic similarities between amyloid and gamma globulin, and between amyloid and Bence Jones protein and other myeloma proteins (Vazquez and Dixon, 1956; Osserman, 1959a; Magnus-Levy, 1952), particularly the 7S and 19S fractions. However, in experimental amyloid deposition following prolonged antigenic stimulation, the abnormal substance remains in the involved area instead of entering the general circulation, suggesting a difference from normal gamma immunoglobulins (Osserman, 1961).

(3)

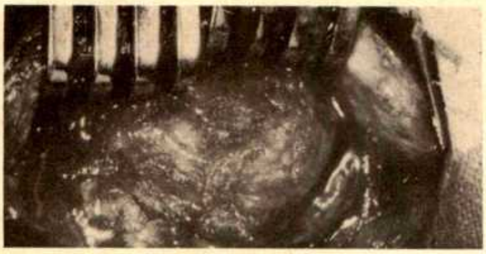

FIG. 3 *Surgical exposure of amyloid mass, left orbit*

(4)

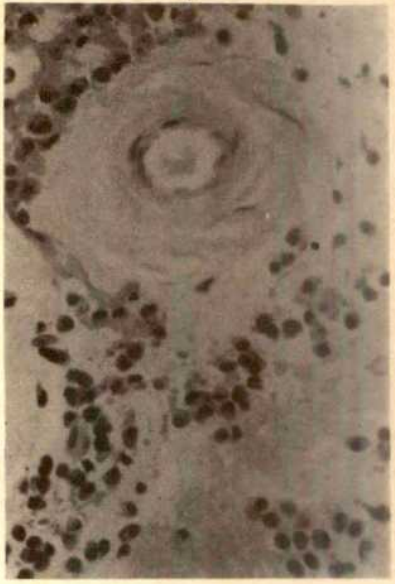

FIG. 4 *Plasma cell accumulation in vessel walls and in surrounding amyloid-infiltrated orbital tissues. Haematoxylin and eosin.* × 384

(5)

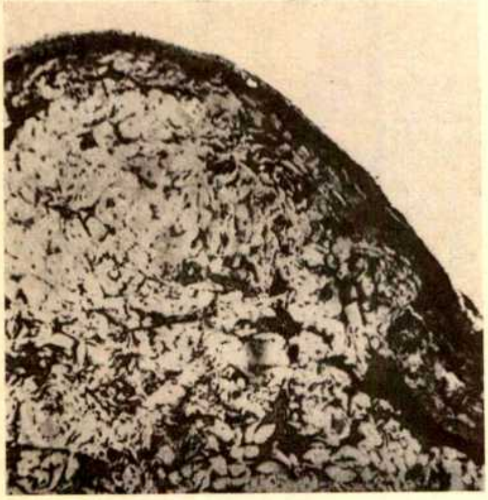

FIG. 5 *Conjunctival biopsy, left eye. Extensive amyloid deposition. Haematoxylin and eosin.* × 40

It has been customary to classify amyloidosis into primary and secondary forms, although this is often difficult because of incomplete understanding of the cause and abnormal chemistry of this condition. One classification is given in the Table (overleaf).

Grossly, amyloid-infiltrated tissue is firm, pale, and waxy. Histologically, amyloid is an amorphous eosinophilic substance with characteristic, although at times non-uniform, staining reactions. It most notably involves small arteries and is also found as nodular deposits in mesenchymal tissues. In a single case there is very little uniformity of involvement.

The diagnosis of amyloidosis is generally considered to be most reliably made by biopsy of suspected organs (tongue, rectum, liver, kidney, bone marrow, and peripheral nerve). The Congo red test is much less reliable and not without danger. Plasmacytosis of the bone marrow is a frequent finding, in both primary and secondary forms. The plasma cells are normal in appearance and need not indicate an underlying myelomatosis (Conn and Sundberg, 1961).

Ocular involvement may be found in both primary and secondary amyloidosis. Conjunctival infiltration is usually a feature of the localized form, either associated with previous trachoma (Mathur and Mathur, 1959) or as a plasmacytoma. The localized ocular form affects young adults, is bilateral in two-thirds of cases, and usually involves both the bulbar and palpebral conjunctivae to a massive extent, with late involvement of the tarsus.

Table *Classification of amyloidosis*

I. Primary No preceding disease; involves mesodermal tissue. Mainly involves heart, gastrointestinal tract, lymph nodes, and smooth and striated muscle

- **A.** Generalized
- **B.** Familial: peripheral neuropathy
- **C.** Respiratory
  - (1) Tumorous: Single or multiple nodules
  - (2) Diffuse

II. Secondary With predisposing disease, usually a chronic infection; also Hodgkin's disease, rheumatoid arthritis. Involves spleen, liver, kidneys, adrenals. Kidneys may also be involved in primary form

---

III. Senile cardiac

IV. Associated with multiple myeloma

V. Localized amyloid tumours Bladder, pharynx, larynx, urethra, eye

---

Ptosis due to tarsal and/or levator muscle infiltration has been reported (Guerry and Weisinger, 1960; Richlin and Kuwabara, 1962). Corneal (McPherson, Kiffney, and Freed, 1966) and vitreous opacities have been described. The vitreous deposits are considered specific in appearance and may precede by many years any clinical evidence of generalized amyloidosis (Kaufman and Thomas, 1959). Retinal periarteritis has been noted (Falls, Jackson, Carey, Rukavina, and Block, 1955).

Many investigators believe that some cases of "primary" amyloidosis are actually instances of occult myeloma or, more generally, of plasma cell dyscrasia, without other clinical evidence. The tissue infiltrates can precede by years the overt manifestations of myeloma. This is especially true in cases that show either Bence Jones proteinuria or hyperglobulinaemia, as did this patient. This observation relates more to generalized amyloidosis than to its localized or familial forms (Osserman, 1959a; Osserman, 1961; Kyle and Bayrd, 1961). The immunochemical relationship of these substances to amyloid and myeloma globulin has already been mentioned. Osserman noted that there was a group of myeloma patients with initially normal skeletal radiographs, who showed proteinuria without renal insufficiency and with evidence of abnormal infiltrates in various tissues (Osserman, 1959b). Cohen (1967) reviewed current thinking concerning the experimental and clinical aspects of amyloidosis.

It is recognized that generalized amyloidosis has not been excluded in this patient; however, regardless of the presence or absence of associated disease, involvement of the orbit by amyloid is an extremely unusual condition. Coats (1915) described a case in which increasing proptosis, reduction of vision, induration and nodular hypertrophy of the conjunctiva, and loss of all motility occurred over a 16-year period. Optic atrophy was noted, but amyloid change was found only in the ciliary muscle, the episclera, and the dural sheath of the optic nerve.

Picó (1961) reported two cases of amyloidosis of the conjunctiva, in which hypothyroidism appeared 6 to 8 years after the first evidence of ocular amyloid. Picó suggested that the primary conjunctival changes might have been myxoedematous infiltration, preliminary to the development of amyloid through changes in chemical composition.

In the present patient, there was no evidence of hypothyroidism during a 10-year interval from the onset of the orbital disease.

Mishra (1962) called attention to the possible role of trauma in the aetiology of localized amyloid change.

The most unusual feature of the present case is that the conjunctiva, although extensively involved in the left eye, apparently became so after the orbital involvement, as evidenced by the fact that the initial manifestation was proptosis; this is in contrast to the usual sequence of events in ocular amyloidosis, suggesting a primary orbital origin. Moreover, the contralateral orbit is now showing a mass with as yet no grossly visible evidence of conjunctival infiltration; biopsy of this tissue has not been allowed by the patient.

Summary

A 55-year-old Negro male had a 10-year history of progressive proptosis of the left eye, with immobility, conjunctival hypertrophy, and decreased vision. Study of the involved tissues, after an initial diagnosis of chondroma, revealed the presence of amyloid. The mass recurred and reached its former size despite an almost total removal; this has been noted in other case reports. Examination of the contralateral orbit has suggested the presence there of a similar involvement. A detailed systemic investigation was undertaken, although biopsies of other organs could not be obtained. A classification of amyloidosis is given, and the apparent rarity of orbital amyloidosis is noted.

Immunofluorescence studies were obtained through the courtesy of Dr. Alan Solomon, Rockefeller Institute New York City. Photomicrographs were supplied by Dr. Andrew P. Ferry.

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Techniques available in reconstructive surgery of the eyelid

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Reconstructive surgery of the eyelids is undertaken in cases in which lid restoration is indicated after the excision of tumours, or after injury, or because of congenital abnormalities.

Utilization of the avulsed flap is recommended after trauma if this is at all feasible. The repair should be performed as soon as possible, but reasonable delay is no contraindication and a successful take with a time lapse of up to 36 hours has been seen at this clinic in the current year. Figs 1 and 2 illustrate the preoperative and postoperative features of a case treated by Dr. Alston P. Callahan, in which 12 hours elapsed before the avulsed flap was replaced.

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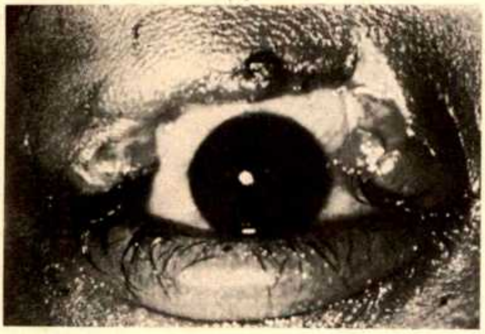

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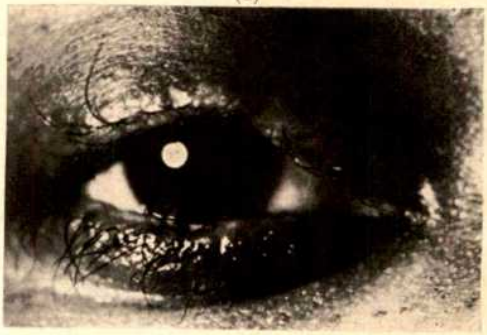

When excision of eyelid structure is indicated, the surgeon should remember that up to one-third of the horizontal dimension can be sacrificed with impunity.

Manipulation of the temporal portion with a skin hook allows the surgeon to estimate if undue tension will be present on the suture line. In such circumstances cantholysis (Figs 3, 4, and 5) may be performed by direct exposure, or by the indirect method which produces added flexibility, allowing the incision to be closed adequately. By this technique, a wedge of up to 10 mm. in size has been resected and closed adequately.

Closure is effected by inserting buried interrupted 6–0 silk sutures in the pre-tarsal fascia (Fig. 6). Three sutures of similar size are used in the intermarginal strip. The first approximates the posterior margin and the second the anterior border; the third suture controls the accurate alignment of the grey line. The needle of each suture should emerge through the lid substance about 2 mm. from the line of incision. Before completing the tie on the second suture, the other tied border sutures are passed through this to avoid postoperative abrasion of the cornea. The accurate approximation of these three sutures guarantees a successful surgical result. Finally, the skin incision is closed with fine silk or chromic catgut.

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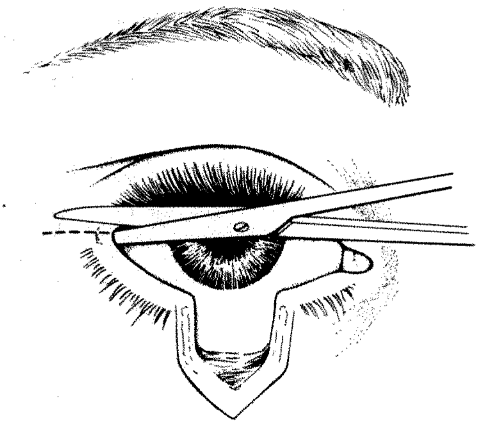

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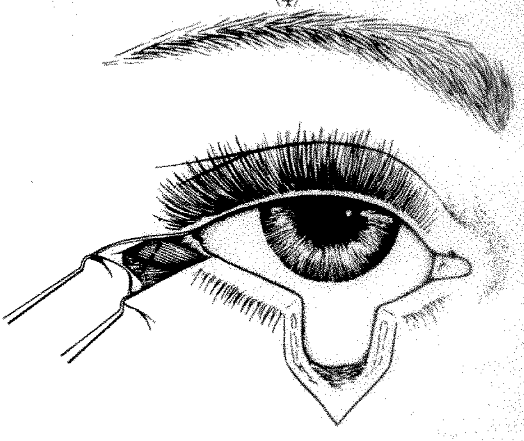

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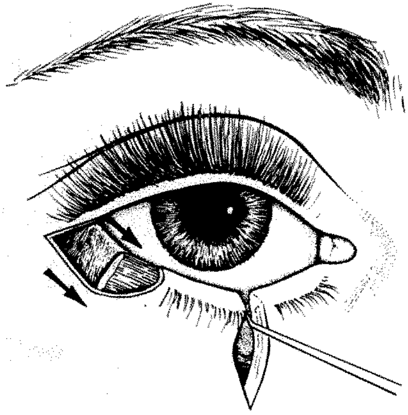

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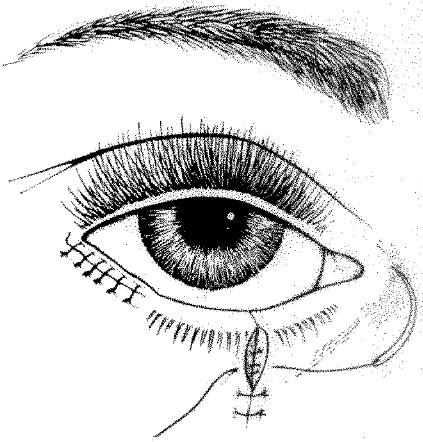

In the presence of larger defects (Fig.7), several techniques are available; lower eyelid reconstruction is best performed with a tarso-conjunctival slide from the upper lid (Fig. 8), the basic principles of which were elaborated by Landolt and Hughes (Hughes, 1954).

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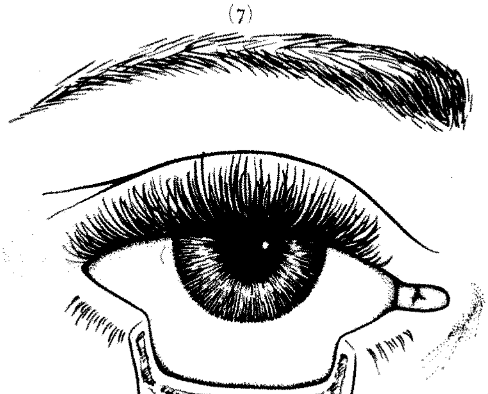

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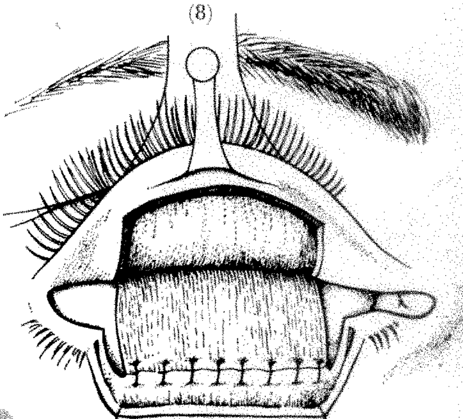

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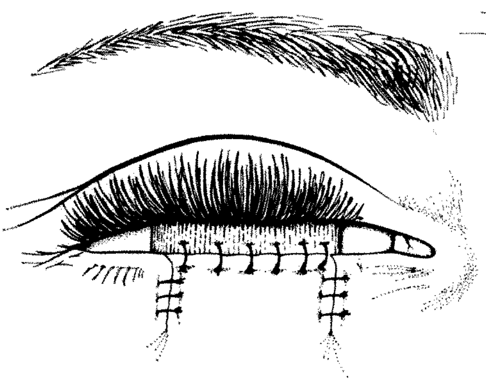
An Erhardt clamp inverts the upper lid and a flap of tarsus is prepared of horizontal span slightly less than the defect. Because it is imperative to preserve the integrity of the lid margin and the marginal arterial arcade, the initial incision is located 3 mm. behind the border of the upper lid. Earlier writers described a splitting of this border, but such a modification can result in entropion and trichiasis with all their distressing sequelae, and is nowadays not recommended. Preparation of a flap which is too wide results in a sagging lower lid. Dissection of the tarsal flap is in the plane of the pretarsal fascia and is carried upwards between Mueller's muscle and the levator palpebrae superioris aponeurosis. This results in a freely mobile flap which is taken down and sutured to the conjunctiva of the lower fornix with interrupted 6–0 chromic catgut sutures. Insufficient dissection producing limitation of mobility results in vertical shortening and increased arching of the upper eyelid postoperatively. Firmer anchorage is obtained by preparing a slot (Fig. 8) which allows the vertical margins of the advanced flap to interdigitate into the lower lid. Double-armed 6–0 silk sutures tied anteriorly over cotton-wool pledgets accurately position the advanced tarsus in these grooves.

A full-thickness stamp skin graft is obtained from the retroauricular area or the upper lid of the other eye; this is fashioned and sutured in position with fine silk sutures and a telfa dressing is applied. Undermining an advancement flap with relaxation triangles is an adequate substitute (Fig. 9) where redundant skin is present in older patients.

(9)



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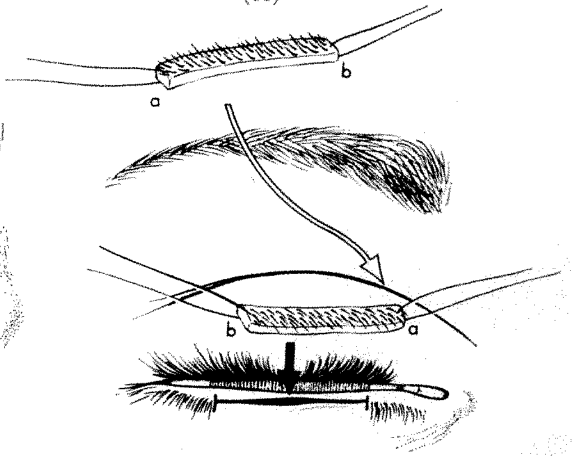
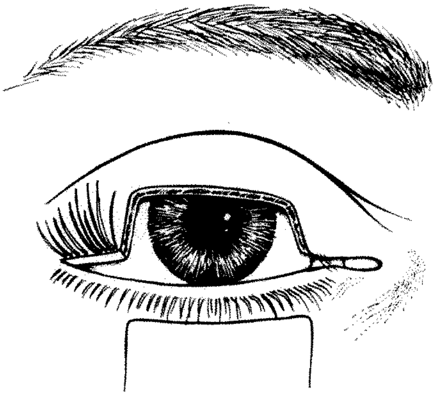


After this stage, a cilia graft can be undertaken at 4 weeks. This improves the appearance and stability of the eyelid margin. An incision shaped like a capital I is performed parallel to the new margin and the bed prepared (Fig. 10). The eyebrow is grasped firmly to produce haemostasis and a strip of full-thickness skin four lash roots in breadth is excised and sutured into its recipient site. After 3 weeks, the eyelids are separated by scissors section and any irregularities are trimmed into proper perspective. If the patient is not desirous of having cilia grafted, the blepharrhaphy may be opened 4 weeks postoperatively.

Large defects in the upper lid require a different approach, as the anatomical limitation of the tarsus of the lower lid makes it less readily available for advancement. A Cutler–Beard bridge flap technique is then to be preferred (Cutler and Beard, 1955). Once again, preserving the integrity of the lid margin, a full-thickness incision is prepared as illustrated (Fig. 11). To control the line of incision, it is advisable to do this as a two-step procedure first from the external and then the internal aspect. A lid plate can be used to maintain stretch on the eyelid or a contact lens shell can act to protect the cornea. A satisfactory flap is prepared by adding the vertical parallel incisions, and this is taken under the bridge of the marginal strip (Fig. 12) to replace the upper lid defect. Interrupted 5–0 plain catgut sutures approximate the conjunctiva of the lower lid with conjunctiva and Mueller's muscle fibres above. The advanced orbicularis muscle is approximated to the levator aponeurosis and septum orbitale, and the skin layer is closed with silk sutures.

(11)



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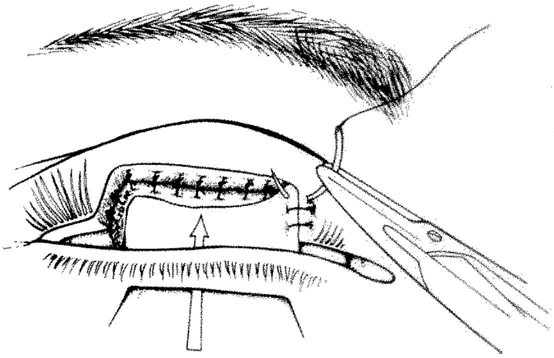
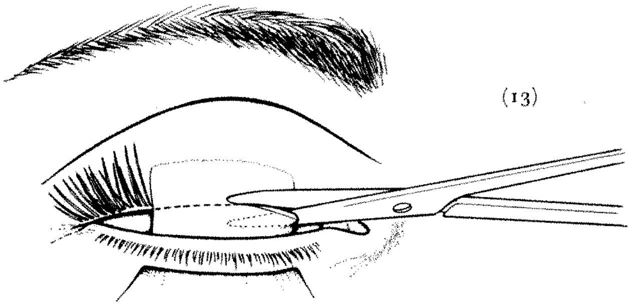


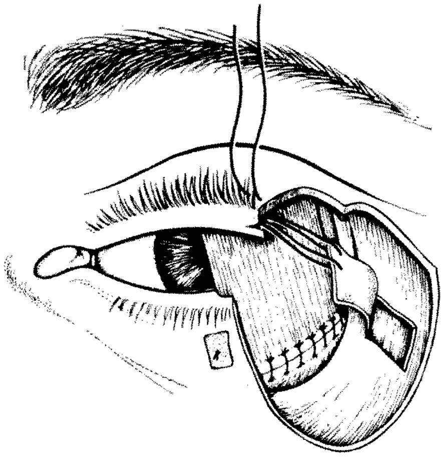
There is no need to close the inferior margin of the bridge flap as this will be covered rapidly by epithelial proliferation. Attempts to suture this are dangerous and impairment of circulation may result. The wound is dressed with telfa and a light pressure pad is applied. Too firm a dressing can produce circulatory embarrassment. The passage of time results in an increase in length of the advancement flap so that it is approximately doubled within 4 weeks. At this stage, grafting of cilia may be performed or, if this is not desired, the blepharrhaphy may be opened with scissors (Fig. 13) and the two components of the lower lid aligned and sutured in place.



(13)

Excision of neoplasms involving the medial or lateral canthi pose special problems to the ophthalmologist, but basically the same principles are applied. In lateral canthal surgery (Fig. 14) a trick manoeuvre of fashioning a flap of orbital periosteum is recommended. This results in an artificial lateral canthal ligament which will give proper alignment of the palpebral fissure. Similarly, the stump of the medial canthal ligament can be used in surgery in this region (Fig. 15). Advancement skin flaps are also employed in these circumstances.

(14)



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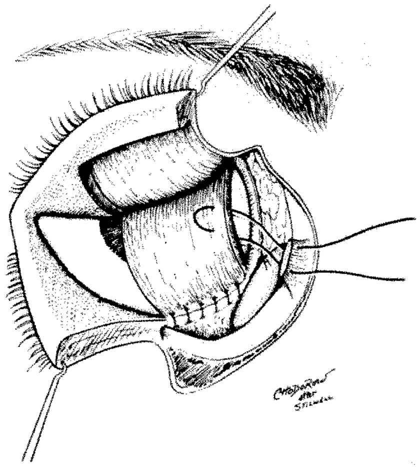
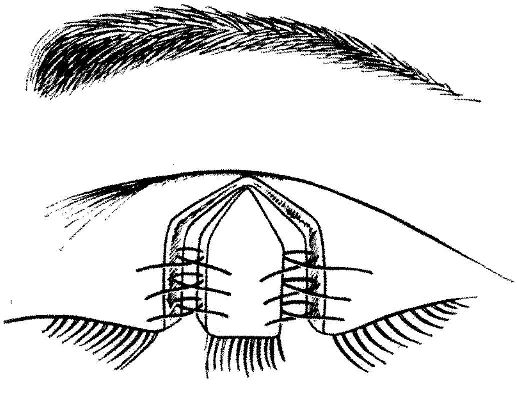


A number of ingenious pedicle grafts and rotation flap techniques are available for reconstructive surgery of the eyelids (Mustardé, 1966). These can be utilized when it is preferable to keep the eye open as, for example, if the contralateral eye is diseased. The consensus of opinion of most ophthalmic plastic surgery clinics in North America, however, favours the earlier-mentioned techniques. These procedures pose no great technical problem to the ophthalmic surgeon with his intimate knowledge of the relevant regional anatomy. They are simple and brief techniques and have the advantage that the cosmetic appearance and texture are approximated, when the principle of replacement of eyelid by eyelid structure is followed. Scarring of tissue is less likely with skin of the orbital region as compared with adjoining zones. Large sliding or rotation flaps enhance this scarring potential in eyelid surgery, and they are especially not favoured for patients prone to keloid formation or for the Negro population. Advancement flaps offer assistance in partial-thickness injuries to the eyelid and can be used effectively in suitable cases.

Large eyelid defects can also be closed by composite lid grafts (Fig. 16) obtained from the opposite upper lid. A full-thickness wedge of the eyelid is taken, inserted in the resected area, and sutured into place with interrupted fine silk sutures placed in the



(16)

pretarsal fascia. Generally, the donor wedge of tissue is smaller in size than the recipient area. The skin incision is finally closed with 6–0 silk sutures. This technique has recently become very popular, but is in fact a long-established one (Smith, 1959).

The eminent John Wheeler (1939) often taught that ophthalmic plastic surgeons thought complexly and operated similarly. The fundamentals of the approach to reconstructive surgery of the eyelids presented above include a number of techniques available to the surgeon. Regardless of the one of his preference, the overriding principle should be that of simplicity in meeting the challenge of this increasing problem.

We are indebted to Dr. Alston P. Callahan of Birmingham, Alabama, for permission to reproduce photographs of his most interesting case.

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Herpes simplex canalicular obstruction

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The characteristics of herpes simplex (herpes virus hominis) infection of the eyelids, conjunctiva, and cornea have been well documented. This case of canalicular obstruction following primary herpes simplex infection appears to be only the second recorded in the literature, and the first in which the diagnosis was confirmed by serological studies.

Case report

A 16-year-old girl was admitted to Bristol Eye Hospital in May, 1968. For the previous 3 days there had been a painful swelling of the right eyelids associated with a vesicular eruption of the margin of the right upper lid, and shortly before admission some vesicles appeared at the angle of the mouth. The girl's boy-friend had noticed a "cold sore" on his lip 11 days previously. The patient had never experienced any epiphora or excessive watering of the eye before this illness.

Examination

The oral temperature was 101°F. and there was bilateral enlargement of the preauricular, submandibular, and jugular lymph nodes. The right eyelids were oedematous and inflamed and there was ulceration and some vesicles on the margin of the upper lid. The oedema was sufficient to close the palpebral fissure. When the lids were separated, the conjunctiva appeared normal apart from some hyperaemia. The cornea was also normal and there was no staining with fluorescein. There were vesicles at the right angle of the mouth, on the dorsum of the tongue, and on the hard palate, with inflammation of the anterior gingival tissue.

Haemoglobin and white cell count were normal. Erythrocyte sedimentation rate (Wintrobe) was 29 mm. in the 1st hr.

A swab from the mouth yielded a scanty growth of *Streptococcus viridans*, diphtheroid sp., and *Neisseria* sp. Conjunctival swabs from both eyes showed a scanty growth of *Staphylococcus aureus*.

Further discrete vesicles appeared on the right cheek and right upper lid shortly after admission, at which stage the clinical photograph shown in Fig. 1 (opposite) was taken.

Diagnosis

Primary herpes simplex infection with secondary bacterial contamination.

Treatment

5-iodo-2′-deoxyuridine drops were instilled hourly into the affected eye and into the vesicles, and neomycin ointment was applied four times a day to both eyes. Erythromycin 250 mg. 6-hrly was also given. The pyrexia settled 3 days after admission. By the eighth day the patient was able to open her eye completely and the vesicles had almost disappeared. She was discharged from hospital 2 days later.

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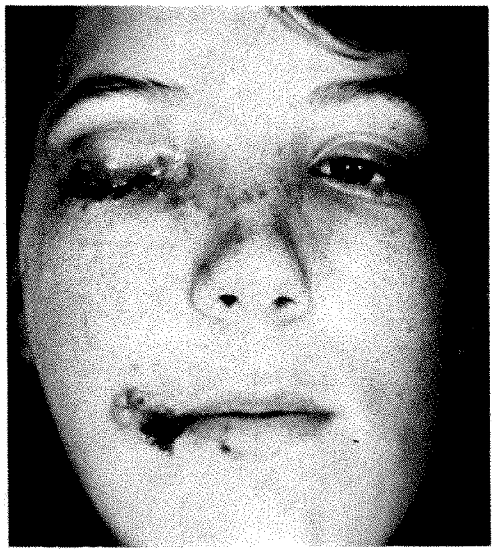

FIG. 1 *Appearance shortly after admission to hospital. Note eyelid oedema and vesicular rash*

Follow-up

When seen in the Out-patients Department 2 weeks later she complained of epiphora, and on syringing the lacrimal apparatus there was some regurgitation of fluid, but some also passed on into the nose. The epiphora persisted, however, and probing 4 months later showed that both canaliculi were completely occluded although the puncta were normal; 6 months after the original illness it was decided to attempt a silicone tube intubation of the canaliculi (Keith, 1968a), but as it was impossible to pass any instrument along either canaliculus the operation was performed as follows:

The lacrimal sac was opened and appeared to be normal, as did the opening into it of the common canaliculus. A pigtail probe was passed retrograde from the sac to the punctum by force but the entire length of both canaliculi was completely occluded (Fig. 2), and there was no evidence that the probe was passing along any anatomical pathway. Monofilament nylon threads were passed from each punctum to the lacrimal sac by threading them through the eye of the probe and from there the nylon threads were passed down the naso-lacrimal duct and a silicone tube intubation was subsequently performed as described by Keith.

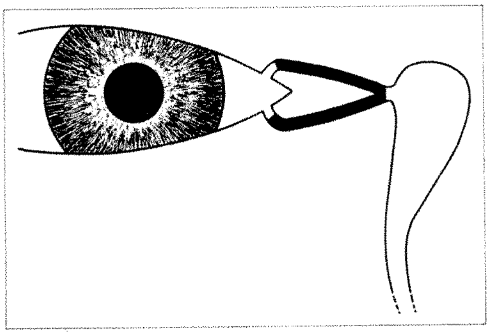

FIG. 2 *Diagram to show extent of canalicular occlusion found at operation*

Postoperatively the epiphora was somewhat improved, but when the silicone tube was removed 6 months later the watering increased again, and examination has shown that both canaliculi are still completely occluded. At present further reconstructive surgery or a neurectomy of the lacrimal gland is being considered. It is interesting to note that one year after the initial illness there was a further eruption of vesicles on the right upper eyelid, but in this instance there was rapid spontaneous recovery.

During and after the illness complement-fixation tests for antibodies to herpes simplex were performed, and the results (Fig. 3) confirmed the clinical diagnosis. Initially no antibodies could be detected, but a month after the onset of symptoms there was a high level of circulating antibodies which gradually subsided.

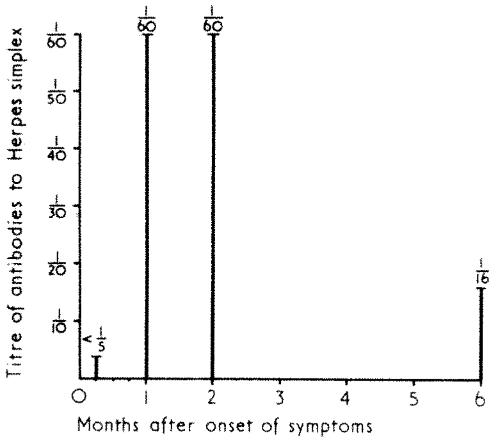

FIG. 3 *Changing titre of herpes simplex antibodies during and after the disease*

Discussion

The lacrimal canaliculus, owing to its narrow calibre, is prone to inflammatory obstruction. This is demonstrated by the risk of occlusion or stenosis after irradiation, and even a long-acting miotic drug (furmethide iodide) has been shown to cause canalicular stenosis (Shaffer and Ridgway, 1951). Isolated canalicular obstruction is a relatively common condition, but the aetiology of most cases remains unexplained (Dalgleish, 1967) and occlusion caused by infective conditions is stated to be relatively rare (Werb, 1966).

Mycotic infection has been reported as a cause of obstruction but the mechanism appears to be a blockage of the lumen by debris and fungi rather than a narrowing of the canaliculus itself, as is shown by the response of these cases to irrigation with antibiotics and curettage (Pine, Hardin, Turner, and Roberts, 1960). (One of the patients with actinomycosis of the canaliculus reported by Pine and Hardin also had a stricture of the lumen, but the patient had previously had an attack of smallpox.)

Bacterial canaliculitis has also been occasionally described. There have been a few case reports of canalicular obstruction caused by Vincent's organisms (a mixed infection of fusiform bacilli and spirochaetal organisms) (Burns, Macnie, Pfeiffer, and Locatcher-Khorazo, 1958; Huysmans, 1962), but all these patients responded to local antibiotics and curettage. There is an isolated report of a case of *Pseudomonas pyocyaneus* infection of the canaliculus, but this also responded to similar measures (Awasthy and Agrawal, 1963). It thus appears that a genuine canalicular occlusion (*i.e.* one caused by narrowing of the lumen and not by blockage by inspissated debris) is not caused by mycotic or bacterial infection.

By contrast it has been shown that viral infections may cause canalicular occlusion, although for most viruses except trachoma the number of case reports is very few. Obstruction due to trachoma has frequently been described. A radiological survey showed that 18 per cent. of cases had narrowing of the canaliculi (Gall, 1961), and Charamis (1957) stated in a review that the incidence of canalicular stenosis in trachoma varied from 0·5 to 80 per cent. according to different reports and different places.

Bouzas (1965, 1960) reported two cases of obstruction after ophthalmic herpes zoster and four after vaccinial conjunctivitis. Werb (1969) mentioned two cases of previous smallpox and chickenpox causing canalicular obstruction. A search of the literature revealed only one previous case report of obstruction following herpes simplex infection (Bouzas, 1965), although Keith (1968b) mentioned one case without giving any details.

In the case reported here there was an unusually severe primary herpetic infection of the eyelids, face, and mouth, with no obvious clinical invasion of the cornea and conjunctiva, which was followed by gradual total obliteration of both canaliculi. The diagnosis apart from clinical evidence was confirmed by the changing level of antibodies to herpes simplex in the patient's serum.

It could be argued that the occlusion was not caused by the virus infection but by the secondary bacterial invasion with *Staphylococcus aureus*; but there was never any clinical evidence of bacterial conjunctivitis, *i.e.* no mucopurulent discharge, and also the organism was cultured bilaterally. In the absence of any evidence of canalicular occlusion following primary staphylococcal conjunctivitis, it is unreasonable to implicate this organism in this instance where it was only a secondary invader.

It could also be possible that the occlusion was caused by the treatment with 5-iodo-2'-deoxyuridine (IDU), as Patterson, Fox, Davies, Maguire, Sellers, Wright, Rice, Cobb, and Jones (1963) showed, in a series of 198 patients with dendritic ulcers treated with IDU, that occlusion of the puncta occurred twice. However, in both cases, the occlusion involved only the puncta and was temporary, unlike the occlusion in the present case. It is also possible that the occlusion reported by Patterson and others (1963) was caused not by the IDU but by the herpes simplex infection.

Although recent surveys have shown a decrease in the percentage of adults with neutralizing antibodies to herpes simplex (Southam, Colley, and Clarke, 1968), infection with this virus remains extremely widespread and recurrent attacks at the same site as the primary eruption are very common. It is possible that the case described here is just an isolated clinical manifestation of herpes simplex which was brought about by the severity of the infection, but it is also possible that it represents the tip of the iceberg of a much larger number of patients who have herpes simplex virus established in the lacrimal canalicular mucosa, eventually causing stenosis and obstruction from recurrent attacks of low-grade infection. This rather tenuous hypothesis could perhaps be proved or disproved by statistical comparison of herpes simplex antibody studies in patients with canalicular stenosis and a group of matched controls. The most significant proven cause of inflammatory canalicular obstruction appears to be virus infection; and in non-trachomatous areas, the herpes simplex virus, by nature of its widespread incidence and tendency to recurrent infections, could be a significant factor.

It is also worthy of note that, if one had been aware of the final outcome of this case at an earlier stage in its clinical course, the passage of a silicone tube at the first sign of narrowing of the canaliculi might have preserved their patency.

Summary

A case of lacrimal canalicular occlusion following a severe herpes simplex infection is described. Although this is only the second case reported in the literature, it is suggested that herpes simplex infection may be a significant cause of canalicular obstruction. The literature concerning other infective causes of such an obstruction is briefly reviewed.

I wish to record my thanks to Mr. C. G. Tulloh, under whose care the patient was admitted, and also to Dr. R. G. Smith of the Bristol Dental Hospital, who supplied the material for Fig. 3 and who has reported on oro-dental aspects of this case.

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Vasogenic origin of visual field defects and optic nerve changes in glaucoma

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Many authors have speculated upon the possibility of a vasogenic origin for the visual field defects, optic disc cupping, and cavernous degeneration in glaucoma, but the exact mechanism has remained obscure. In our recent experimental studies (Hayreh and Perkins, 1968, 1969; Hayreh, 1969) we discovered the important role of the ciliary circulation, particularly the contribution of the choroidal circulation to the prelaminar part of the optic disc and the retrolaminar part of the optic nerve.

In fluorescein fundus angiographies the choroidal vascular bed and its contribution to the optic disc are normally masked by the overlying dense retinal vascular bed. In our previous studies to assess the choroidal circulation and the changes therein which are associated with ocular hypertension, the retinal circulation was experimentally occluded in one eye of a cynomolgus monkey and the findings reported as a part of other investigations (Hayreh and Perkins, 1969; Hayreh, 1969). This method has since been employed in a further series of experiments and has provided further information on the subject.

Material and methods

In eight eyes of five cynomolgus monkeys the central retinal artery was exposed by lateral orbitotomy and occluded near its site of entry into the optic nerve. Fluorescence fundus angiography was then performed after an injection of 0·15 ml. 5 per cent. sodium fluorescein solution into the common carotid artery on the same side. The fundus was photographed every 0·8 sec. by a Zeiss fundus camera adapted for fluorescence angiography, starting from the time of injection of the dye and continuing until the end of the transit of the dye.

Fluorescence fundus angiographies were repeated on five eyes at normal intraocular pressure and at pressures of 70, 30, and 15 mm. Hg (Fig. 1). In one animal fluorescence angiography was first performed in the left eye at the normal intraocular pressure (about 12 mm. Hg) and at 70 and 40 mm. Hg (Fig. 2); and then in the right eye at the same intraocular pressures (Fig. 3). The systemic arterial blood pressure was then lowered rapidly by the intravenous injection of Lignocaine solution and fluorescence angiography was repeated in the right eye at intraocular pressures of 70, 40, and 20 mm. Hg (Fig. 3). The blood pressure was allowed to recover to 110/60 mm. Hg and fluorescence angiography was repeated at an intraocular pressure of 15 mm. Hg in the right eye.

In another monkey, in which the blood pressure had fallen to 35/15 mm. Hg owing to surgical shock, fluorescence angiography was performed in the right eye at the normal intraocular pressure, 50, 20, and 5 mm. Hg.

The systemic blood pressure was measured by cannulating the femoral artery in two animals (3 eyes), and was recorded on a Sanborn recorder.

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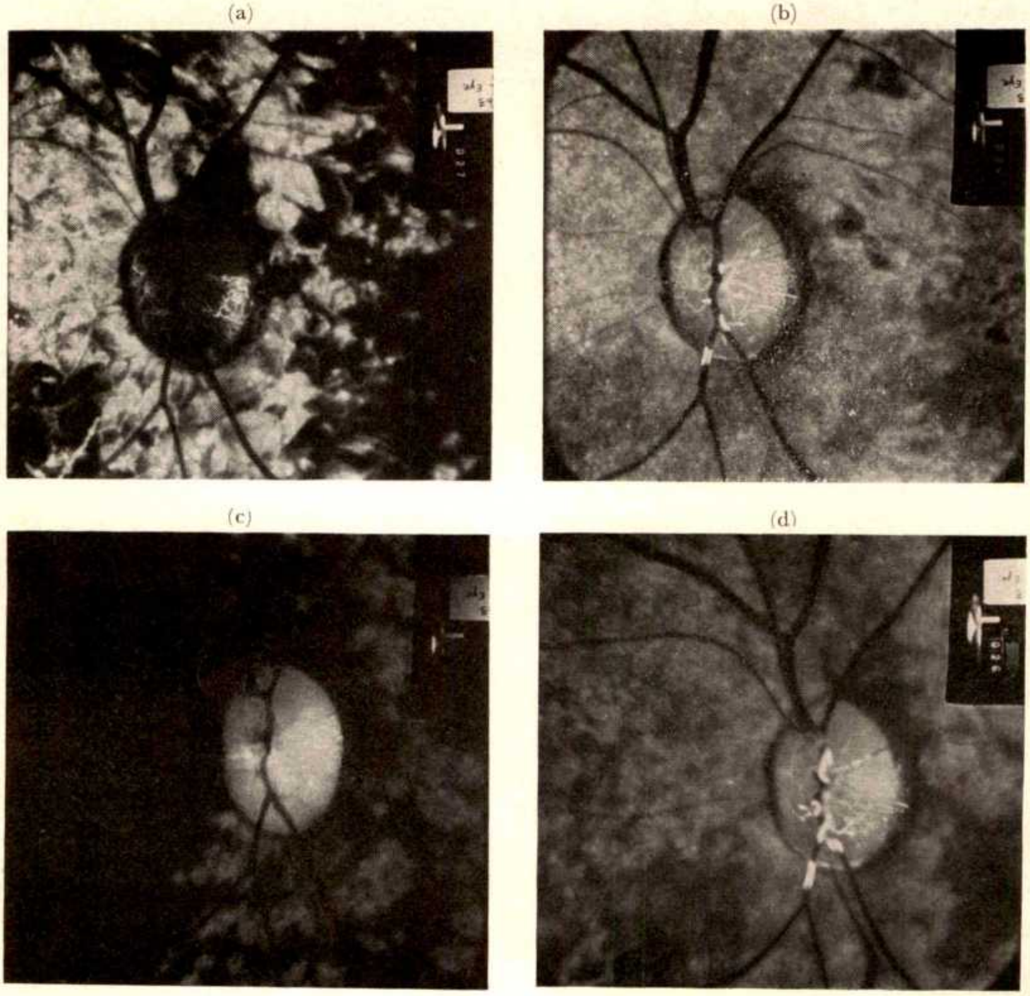


FIG. 1 *Fluorescence fundus angiograms of left eye of a cynomolgus monkey (after experimental central retinal occlusion) at normal* (a, b), 70 *mm. Hg* (c), *and* 30 *mm. Hg* (d) *intraocular pressures*
(b), (c), *and* (d) *are comparable phases of circulation of the dye at three intraocular pressures*
(a) *and* (b) *are at* 1·6 *sec. interval, showing pattern of filling of vessels in choroid and optic disc. Choroidal pigment deposit at disc margins obscures underlying choroidal fluorescence in some places*

Observations

In all these fluorescence angiographies the pattern of filling of the choroid in the posterior segment, the peripapillary choroid, and the optic disc was recorded. The results fall into two categories:

(A) Seven eyes of animals with normal or apparently normal blood pressure.

(B) Two eyes of animals in which the systemic arterial blood pressure was very low.

(A) Normal systemic arterial pressure

(1) CHOROID

In most cases the choroidal circulation shows marked variations in the degree of filling. This makes the interpretation of its circulation by fluorescence fundus angiography very

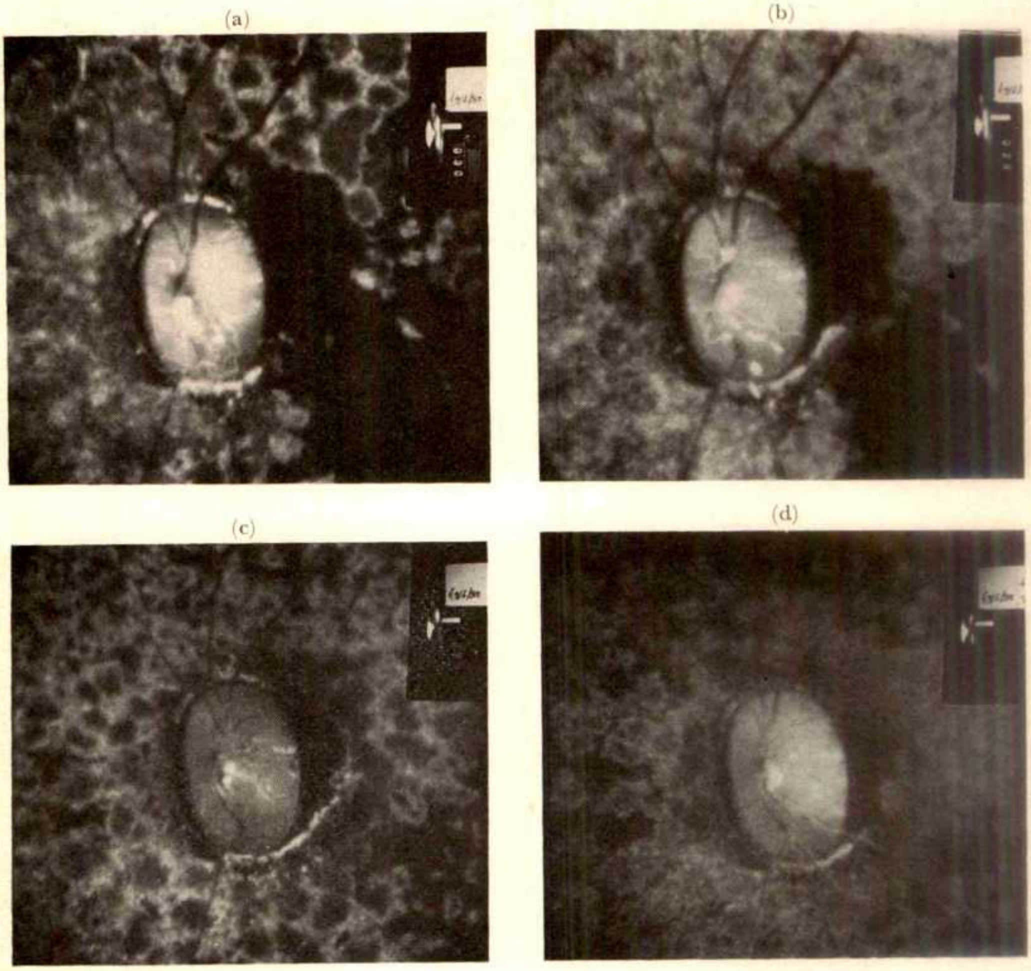
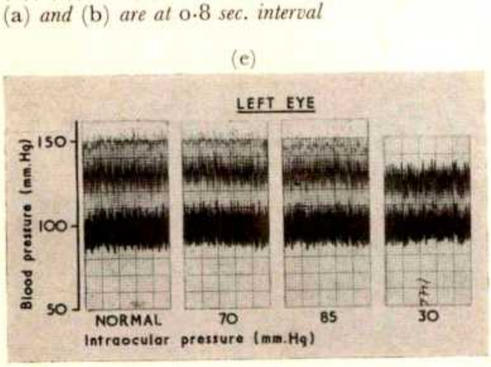


FIG. 2 *Fluorescence fundus angiograms of left eye of a cynomolgus monkey (after experimental central retinal occlusion) at normal* (a, b), 70 *mm. Hg* (c), *and* 85 *mm. Hg* (d) *intraocular pressures*
(e) *shows tracings of systemic arterial blood pressures at three intraocular pressures,* i.e. 150/85 *mm. Hg*
(b), (c), *and* (d) *are comparable phases of circulation of the dye at the three intraocular pressures*
(a) *and* (b) *are at* 0·8 *sec. interval*



Filling defect in temporal peripapillary choroid is a spatial variation

Choroidal pigment deposit at disc margins obscures fluorescence in some areas

difficult, and sometimes erroneous, if a single picture only or a series of pictures taken at prolonged intervals is examined. A series of angiograms taken in quick succession, however, quite often reveals a changing pattern of choroidal filling from picture to picture.

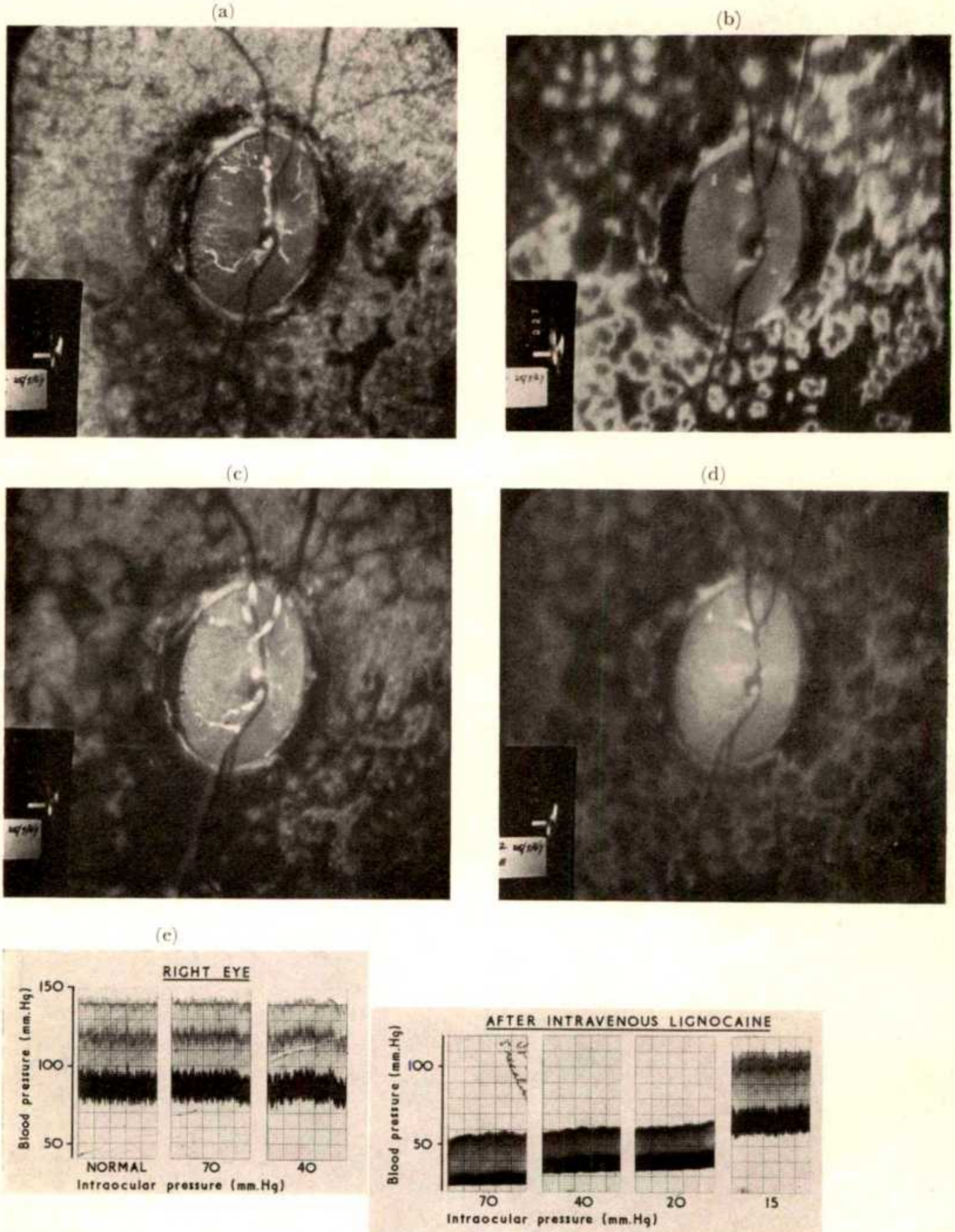


FIG. 3 *Fluorescence fundus angiograms of right eye of a cynomolgus monkey (after experimental central retinal artery occlusion) at normal* (a), 70 *mm. Hg* (b), 40 *mm. Hg* (c), *and* 20 *mm. Hg* (d) *intraocular pressures* (e) *shows tracings of systemic arterial blood pressures at the three intraocular pressures,* i.e. 140/80 *mm. Hg at* (a) *and* (b), 140/75 *mm. Hg at* (c), *and* 62/35 *mm. Hg at* (d)

Choroidal pigment deposit at disc margins obscures underlying fluorescence in some areas

All pictures represent comparable phases of circulation at the various intraocular pressures

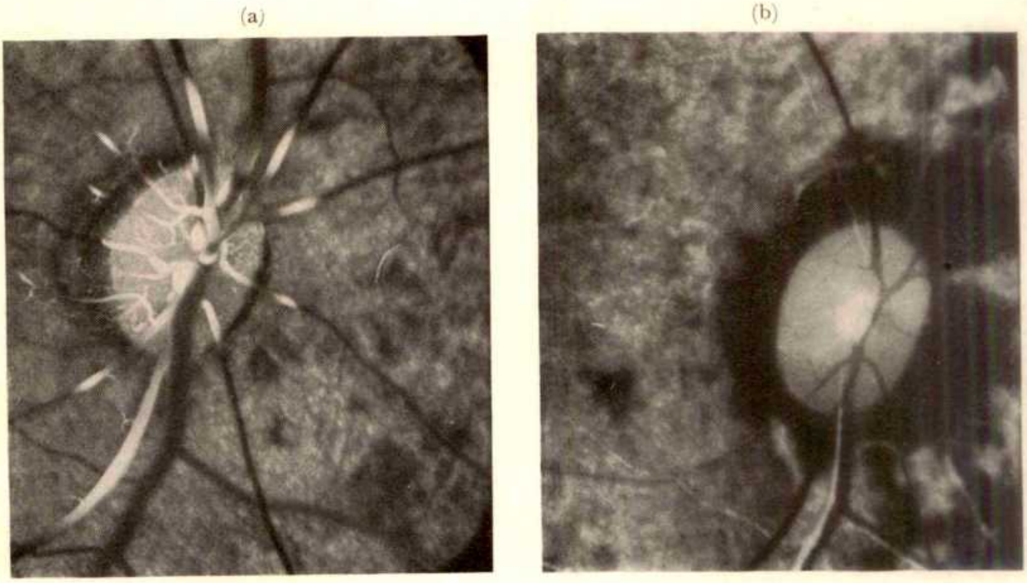


FIG. 4 *Fluorescence fundus angiograms of right eye of a cynomolgus monkey (after experimental central retinal artery occlusion) at normal* (a) *and* 70 *mm. Hg* (b) *intraocular pressures*

Choroidal pigment deposit at disc margins obscures underlying fluorescence in some areas

The appearances after an interval of a few seconds, or even after 0·8 sec., may show a reversal of the filling pattern. The true pattern of choroidal filling can therefore be assessed only by examining the entire transit of the dye in the choroid photographed serially at very short intervals. Many of the variations in the filling of the choroid may be classified as spatial or temporal variations. In the former some areas fill first and empty first, while others fill later and empty later. Temporal variation, in which different transits of the dye show different patterns of choroidal filling, is common. In addition to these variations, rapid serial photography at 0·8 sec. intervals often shows that some areas fill and empty more rapidly than others.

(*a*) *At the normal intraocular pressure* The whole of the choroid filled (Figs 1*b*, 3*a*, 4*a*), though spatial variations were seen in the majority of the eyes, *i.e.* some parts filled earlier and emptied earlier than others. The peak filling of the choroid and its maximum fluorescence were usually reached in about 3 to 4 sec., rarely after longer intervals.

(*b*) *At* 70 *mm. Hg intraocular pressure* There was delay in filling of the choroid and the transit time of the dye was prolonged. The filling tended at first to have a honeycomb pattern and was sometimes patchy (Figs 1*c*, 2*c*, 3*b*); at peak filling, however, the fluorescence was usually denser than at the normal intraocular pressure, presumably because of marked venous congestion. Spatial variations in filling were still present. In two out of eight eyes the watershed areas between the distribution of the two main posterior ciliary arteries did not fill at this pressure (see Fig. 12*b* in Hayreh, 1969).

In an eye in which the intraocular pressure was raised to 85 mm. Hg (Fig. 2*d*), with the systemic blood pressure at 150/85 mm. Hg, these changes in the choroid were more pronounced than at 70 mm. Hg (Fig. 2*c*) in the same eye, *i.e.* there was slower filling with a longer transit time and denser fluorescence.

(*c*) *At* 30 *mm. Hg intraocular pressure* The filling and emptying of the choroid was slightly slower than at the normal pressure in the same eye, but much faster than at 70 mm. Hg. The honeycomb pattern was less marked than at 70 mm. Hg (Fig. 1*d*). The filling defect seen in the watershed areas in the two eyes at 70 mm. Hg was not seen at this pressure. In two eyes in animals with systemic blood pressures of 140/75 and 130/85 mm. Hg, no significant change in the choroid was detected at this pressure and filling was almost the same as at the normal intraocular pressure. Spatial variations in the filling were seen.

(2) PERIPAPILLARY CHOROID

The different types of variation in the filling of the choroid were also seen in the peripapillary choroid (p. 462).

(*a*) *At the normal intraocular pressure* The peripapillary choroid filled well (Figs 1*b*, 3*a*, 4*a*). Four eyes, however, showed a poor and late filling of one portion:

(*i*) In the upper and lower parts in two eyes;
(*ii*) In the infero-nasal part in one eye;
(*iii*) In the supero-nasal part in one eye.

(*b*) *At* 70 *mm. Hg intraocular pressure* Filling defects in the peripapillary choroid were seen in four of six eyes, in which a detailed examination of this region was possible. In the other two eyes the systemic blood pressure was in the region of 140/80 mm. Hg. The distribution of the filling defects in the peripapillary choroid was as follows:

(*i*) No filling of the peripapillary choroid above, below, and nasal to the optic disc in one eye;
(*ii*) No filling of the entire peripapillary choriod all round the optic disc in one eye (Fig. 4*b*);
(*iii*) No filling of the peripapillary choroid except in the supero-temporal sector in one eye;
(*iv*) No filling of the temporal part of the peripapillary choroid in one eye (Fig. 2*c*). This eye had some peripapillary choroidal atrophy in this sector. At the normal intraocular pressure, however, it filled normally, though it showed a spatial variation in the temporal region.

(*c*) *At* 30 *mm. Hg intraocular pressure* Complete obliteration of the peripapillary choroid was not seen at this intraocular pressure (Fig. 1*d*). In four out of six eyes some sectors showed late filling with rapid emptying:

(*i*) The entire peripapillary choroid;
(*ii*) The lower part of the peripapillary choroid;
(*iii*) The area round the optic disc, except in the temporal part;
(*iv*) The nasal part of the peripapillary choroid.

(3) OPTIC DISC

(*a*) *At the normal intraocular pressure* The entire disc filled, with the temporal sector containing the maculo-papillar bundle region showing the maximum fluorescence in all the bundles (Figs 1*a*, *b*, 2*a*, *b*, 3*a*, 4*a*).

In one eye the temporal part of the peripapillary choroid filled very late (Figs 2*a*, *b*); the temporal sector of the disc, however, filled earlier and normally, which indicated that, in this eye, the temporal region of the disc probably filled mainly from the vessels of the underlying lamina cribrosa or possibly from a peripapillary vessel which could not be seen because of overlying pigment. This possible explanation is suggested because in some eyes a circular vessel was outlined round the optic disc.

Fluorescence of the optic disc usually developed in parallel with the choroidal flourescence.

(*b*) *At* 70 *mm. Hg intraocular pressure* The filling of vessels in the optic disc was very much reduced at this pressure. In two eyes no vessels filled at all (Fig. 4*b*); in three eyes there was delayed and very poor filling, and that only in the temporal sector (Fig. 1*c*); in the remaining two the temporal and nasal parts filled—the temporal more than the nasal—but it was a poor and late filling (Fig. 2*c*, 3*b*). In these two animals, the systemic arterial blood pressure was 150/85 and 140/80 mm. Hg respectively. In one of them, when the intraocular pressure was raised to 85 mm. Hg (with systemic arterial blood pressure at 150/85 mm. Hg), only the vessels in the temporal sector filled, and even these filled late and very poorly (Fig. 2*d*).

Fluorescence of the optic disc usually developed in parallel with the choroidal fluorescence.

(*c*) *At* 30 *mm. Hg intraocular pressure* The vessels of the optic disc filled well but slightly less than at the normal intraocular pressure (Fig. 1*d*, 3*c*). In a few instances there was no significant difference from the filling at the normal intraocular pressure.

(B) Low systemic arterial pressure

In one animal experimental systemic arterial hypotension was induced by the intravenous injection of Lignocaine solution; the filling of the choroid, peripapillary choroid, and the optic disc in the right eye at different intraocular pressures is shown in Table I.

Table I *Pattern of filling of vessels of choroid and optic disc in right eye of a cynomolgus monkey at different intraocular pressures and systemic arterial blood pressures*

Fluorescein angiography transit no.	*Pressures (mm. Hg)*		*Filling of*		
	Systemic arterial	*Intraocular*	*Choroidal vessels*	*Peripapillary choroidal vessels*	*Optic disc vessels*
I (Fig. 3*a*)	140/80	Normal	Whole choroid filled Maximum in 3rd exposure	Normal	Whole disc filled
II (Fig. 3*b*)	140/80	70	Slow with delayed transit Maximum in 7–8th exposure	No significant defect Delayed	Poor and slow Temporal side only filled
III (Fig. 3*c*)	140/75	40	Whole choroid filled Maximum in 6th exposure Transit slightly more prolonged than at normal intraocular pressure	No significant defect	Slightly less than normal but much better than at 70 mm. Hg
IV	57/25	70	None	None	None
V	60/32	40	None	None	None
VI (Fig. 3*d*)	62/35	20	Very similar to II		
VII	110/60	15	Rapid filling of whole choroid Maximum in 3rd exposure Shorter transit time than in I	No defect	Difficult to assess owing to marked fluorescence of optic disc by this stage

In the second animal, in which the systemic arterial pressure was 35/15 mm. Hg, the choroid and optic disc showed normal filling at normal intraocular pressure, but there was no filling of the choroid and disc at intraocular pressures of 50 and 25 mm. Hg. When the intraocular pressure was lowered to 5 mm. Hg the choroid and disc filled normally (Table II).

Table II *Pattern of filling of vessels of choroid and optic disc in three eyes of two cynomolgus monkeys (Nos* 1 *and* 2 *belonging to one animal) at different intraocular pressures and systemic arterial blood pressures*

Eye no.	*Pressures (mm. Hg)*			*Filling of*	
	Systemic arterial	*Ophthalmic arterial*	*Intraocular*	*Choroidal vessels*	*Optic disc vessels*
1	150/85	110/75	70 (Fig. 2*c*)	Slow with prolonged transit	Less than normal Temporal > nasal
	150/85	110/75	85 (Fig. 2*d*)	Still slower with more prolonged transit	Very poor Some vessels filled in temporal part only
	150/85	110/75	30	Normal with normal transit	Normal
2 (See also Table I)	140/80	100/72	70 (Fig. 3*b*)	Slow with prolonged transit	Poor Only temporal side filled
	140/75	100/68	40 (Fig. 3*c*)	Slightly less than normal	Slightly less than normal
	57/25	42/22	70	None	None
	60/32	44/29	40	None	None
	62/35	45/31	20 (Fig. 3*d*)	Slow with delayed transit	Poor Only temporal side filled
	110/60	80/54	15	Normal	Difficult to assess owing to marked fluorescence of optic disc
3	35/15	25/13	50	None	None
	35/15	25/13	25	None	None
	35/15	25/13	5	Normal	Normal

Discussion

Duke-Elder (1953), stressing the vasogenic factor in glaucoma, stated that "if the be-all and end-all of glaucoma resided in a raised tension and the raised tension itself were dependent upon the efficacy of drainage of the intraocular fluids, then surely the anxieties of five generations of ophthalmologists and the tragedy of blindness that has overtaken countless numbers of their patients could be mechanically relieved by sufficiently enthusiastic surgery". Moreover, Duke-Elder (1955) reported that glaucomatous visual field defects and cupping of the optic disc sometimes occurred without a raised ocular tension, and added that the optic disc and the visual fields may remain normal for a long time with a high tension in the absence of vascular sclerosis. A vasogenic factor in the causation of visual field defects and of changes in the optic disc and optic nerve in glaucoma has been suggested by very many workers (Hayreh, 1970), but there has been much controversy on the vessels involved and the site of the lesion. Most authors consider the involvement of retinal vessels or the arterial circle of Zinn and Haller to be responsible.

Gallois (*cited by* Lauber, 1936) stated that a sustained increase in intraocular pressure compressed the arteries of the optic disc, thus slowing down the blood flow. Reese and McGavic (1942) stressed the importance of the relationship between the intraocular pressure and the retinal blood pressure in the determination of field loss. Lauber (1936) had also suggested this.

Gafner and Goldmann (1955) described how a rise in intraocular pressure resulted in a reduced blood flow in the laminar region and how a similar change was caused by a fall in pressure in the arteries supplying this region. Niedermeier (1957) described the circulatory disturbances in the region of the arterial circle of Zinn and Haller. Harrington (1959, 1964) suggested that glaucomatous visual field defects were the result of diminished blood flow in the anterior optic nerve in the region of the lamina cribrosa and the circle of Zinn and Haller. According to him this circulatory insufficiency in the anterior optic nerve might be brought about by a number of conditions, one or more of which could upset the normal balance between the intraocular pressure and the retinal or ophthalmic arterial pressure, producing hypoxia in the nerve head and resulting in the characteristic glaucomatous field defects. Hypoxia in the nerve head may be due either to a rise in the intraocular pressure sufficient to overcome normal arterial pressure in the arterioles, or to a fall in the blood pressure in the optic nerve head arterioles, so that a normal or slightly elevated intraocular pressure produces hypoxia in the nerve. The fall in blood pressure may be secondary to arterial insufficiency in the ophthalmic artery and its branches, due for example to carotid artery stenosis or occlusion, to arteriosclerotic plaques in the small arterioles at or behind the lamina cribrosa or on the optic disc, or to embolic phenomena. Similarly, Drance, Wheeler, and Patullo (1968) concluded from their clinical studies that the changes produced in chronic simple glaucoma could be due either to markedly elevated intraocular pressure embarrassing the circulation of the optic nerve head and retina independently of other factors, or to extreme circulatory disturbances with no change in the intraocular pressure. They found a low diastolic blood pressure in all patients who showed marked damage to the optic nerve head or visual field defects.

Our previous studies (Hayreh and Perkins, 1968, 1969; Hayreh, 1969) have shown that the ciliary contribution to the optic disc (both from the peripapillary choroid and from the vessels of the underlying lamina cribrosa) is very susceptible to a raised intraocular pressure, to the point of becoming obliterated. The peripapillary choroid was slightly less susceptible than the vessels in the optic disc; this observation has also been recorded by other workers (Gitter, Blumenthal, Galin, and Best, 1969, in man; Ernest and Potts, 1968, and David, 1969, in monkeys). The rest of the choroidal circulation is also susceptible to raised intraocular pressure, though to a smaller extent than the two regions mentioned above. We found no significant defect in the retinal circulation on acute elevation of the intraocular pressure; this contradicts the views of Henkind (1967a, b), Alterman and Henkind (1968), and Kornzweig, Eliasoph, and Feldstein (1968). From our studies it was concluded that, in glaucoma, the primary factor responsible for the visual field defects, optic disc changes, and cavernous degeneration of the optic nerve is the involvement of the choroidal vasculature, especially the peripapillary part thereof and its contribution to the optic disc (Hayreh, 1969).

The present study confirms the previous conclusions (Hayreh and Perkins, 1968, 1969; Hayreh, 1969) and shows that *the amount of filling of the vessels in the optic disc, peripapillary choroid, and the remainder of the choroid is determined by two factors*:

(*a*) *the intraocular pressure*;

(*b*) *the blood pressure in the ciliary circulation.*

In the present study the systemic arterial pressure was taken as a guide to the ciliary blood pressure. In other studies (Hayreh and Edwards, in preparation) on the relationship of the ophthalmic artery pressure and the systemic arterial pressure in rhesus monkeys, it was discovered that the systolic blood pressure in the ophthalmic artery normally varied between 69 and 76 per cent. (average 73) of the systemic systolic arterial pressure, and that the diastolic pressure in the ophthalmic artery varied between 85 and 96 per cent. (average 90) of the systemic diastolic pressure. Applying these ratios between the systemic and the ophthalmic artery pressures, we can estimate the ophthalmic artery pressure in the three eyes of the present series in which the systemic arterial pressure was recorded by cannulating the femoral artery. The filling of the choroid and optic disc at the different intraocular pressures and the systemic and ophthalmic arterial pressures is shown in Table II. These results suggest that, when the difference between the systemic diastolic arterial pressure and the intraocular pressure is about 10 mm. Hg or less, the filling of the vessels in the optic disc is very poor, being seen only in the temporal sector. When the systemic diastolic pressure is lower than the intraocular pressure, there is no filling of the vessels in the disc or choroid. The exact role of the systolic systemic arterial pressure is not clear but, in an eye in which the difference between systemic systolic pressure and the intraocular pressure was 20 mm. Hg, there was no filling of the choroid and optic disc; where there was a difference of 30 to 42 mm. Hg, however, filling of these regions occurred. In the latter two the systemic diastolic pressure was also higher than the intraocular pressure.

It can be concluded from the above observations that a rise in the intraocular pressure or a fall in the arterial blood pressure has a similar effect on the choroidal, peripapillary, and optic disc vessels. The extent of filling of the vessels depends upon the difference between the two: the greater the difference the better the filling, and *vice versa*. This is well illustrated by the eyes with arterial hypotension described in Tables I and II. A similar phenomenon was noticed by Harrington (1959) in patients with arterial hypertension who, on therapeutic lowering of the blood pressure, developed glaucomatous field defects at normal or slightly raised intraocular pressures, a rise in blood pressure leading to partial recovery. McLean (1957) reported a similar experience. Gafner and Goldmann (1955) found a rapid loss of visual field in a case of Addison's disease with arterial hypotension.

In glaucoma, until now, the main emphasis has been placed on raised intraocular pressure, and the management of the condition has been guided solely by the level of the intraocular pressure. The fact that some patients develop typical glaucomatous visual field defects and optic disc changes at normal intraocular pressures, while others develop no ocular defects when the pressure is significantly raised has always been puzzling. The present study has shown that two equally important factors determine the outcome in cases of glaucoma; the intraocular pressure and the arterial blood pressure in the choroidal vessels. Although we have satisfactory methods of measuring the intraocular pressure, there is as yet no known method of measuring the blood pressure in the choroidal vessels.

Ophthalmodynamometry may give some idea of the blood pressure in the central retinal artery and thus act as an indirect means of estimating the ophthalmic artery pressure, and hence the posterior ciliary artery pressures, though the central retinal artery pressure may not necessarily be a true index of the ciliary or choroidal arterial blood pressure. Moreover, with ophthalmodynamometry, it is not possible to determine absolute values for systolic and diastolic pressures in the retinal arteries. This method only makes possible the comparison of the blood pressures in the two eyes of the same individual, *e.g.* in unilateral carotid or ophthalmic artery occlusion or stenosis. Alternatively, the systemic arterial blood pressure may be used as a guide to estimating the choroidal arterial blood pressure, though this again is likely to have many drawbacks.

Thus, it is ignorance of the blood pressure in the choroidal and posterior ciliary vessels which makes correct assessment and management of glaucoma a difficult task. The only satisfactory solution would be to correct the imbalance between the intraocular pressure and the blood pressure in the choroidal vessels, instead of being guided by the level of the intraocular pressure alone.

This imbalance also explains the mechanism of so-called "low-tension glaucoma" or "pseudo-glaucoma", which has been a baffling problem. In this condition, instead of a rise in intraocular pressure there is a fall of blood pressure in the ciliary vessels, but the end-results are the same. Another variety of low-tension glaucoma is seen in arteriosclerotic optic atrophy, where a fall in blood pressure in the optic disc and choroidal vessels, caused by arteriosclerotic changes in the posterior ciliary arteries, upsets the normal balance between the intraocular pressure and the blood pressure in the disc and choroidal vessels. A similar phenomenon will result from any factor producing low blood pressure in the ciliary arteries, ophthalmic artery, or carotid artery, *e.g.* stenosis, occlusion, embolism, or systemic arterial hypotension.

The mechanism of glaucomatous visual field defects, cupping of the optic disc, and cavernous degeneration of the optic nerve is discussed in detail elsewhere (Hayreh, 1969, 1970). The nerve fibre bundle defects and optic disc cupping are due to obliteration of vessels in the prelaminar part of the optic disc and peripapillary choroid. Peripheral constriction of the visual fields and cavernous degeneration of the retrobulbar part of the optic nerve are due to the involvement of the peripheral centripetal vascular system composed of recurrent pial branches from the peripapillary choroid to this part of the optic nerve (see Fig. 1, Hayreh, 1969). Since the peripapillary choroid supplies both the prelaminar part of the optic disc and retrobulbar part of the optic nerve (Hayreh, 1969), its involvement will affect these two regions. The balance between the intraocular pressure and the arterial blood pressure in the choroid, peripapillary choroid, and prelaminar region of the optic disc determines the state of patency of these vessels, and a critical equilibrium exists, particularly in those of the optic disc; lowering of the blood pressure or elevation of the intraocular pressure would have an identical effect.

From these observations, *glaucoma may be defined as a disease wherein the normal balance between the intraocular pressure and the blood pressure in the choroidal vessels supplying the optic disc and retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and the retrolaminar part of the optic nerve, and hence in visual field defects and pathological changes in the optic disc and optic nerve.*

Summary

The effect of raised intraocular pressure on the circulation in the choroid and optic disc was studied by fluorescence fundus angiography in eight eyes of cynomolgus monkeys

after experimental occlusion of the central retinal artery. The findings showed that the balance between the intraocular pressure and the arterial blood pressure in the vessels of the choroid, peripapillary choroid, and prelaminar region of the optic disc determines the state of circulation in these regions. Elevation of the intraocular pressure and lowering of the blood pressure in these vessels have a similar effect. The circulatory disturbances in the optic disc which ensue are responsible for the visual field defects and the optic disc and optic nerve changes in glaucoma.

We are grateful to Prof. E. S. Perkins for providing us with the facilities for this study, to Mrs Anne Roger for secretarial help, and to Mr. Alasdair McDonald for the illustrations.

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Pseudoelastic nature of pterygium

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Elastotic degeneration in cases of pterygium, as in pinguecula, is characterized by the appearance of vermiform, coiled, and knotty fibres which take up elastic stain, but these so-called elastic fibres appear to differ from natural elastic tissue. There are certain skin diseases in which an apparent increase in elastic fibres is seen (Tunbridge, Tattersall, Hall, Astbury, and Reed, 1952). Gillman, Penn, Bronks, and Roux (1954) called these fibres "elastotically degenerated" because they can only mimic the staining character of true elastic tissue. They remain unaffected by the pancreatic elastase, an enzyme discovered by Baló and Banga (1949) which is supposed to have a specific action on such tissue (Hall, Reed, and Tunbridge, 1952).

It was thought in the past that in pinguecula there was an increase in the elastic fibres normally present in the bulbar conjunctiva, but Cogan, Kuwabara, and Howard (1959) proved by the use of pancreatic elastase that they were non-elastic in nature. Vass and Tapaszto (1964) extended this study to pterygium but did not reach a firm conclusion. We therefore undertook the present investigation to find out the precise changes in pterygium tissue deep to the conjunctiva with special reference to the elastic fibres.

Material and methods

The material was obtained from patients who attended the Gandhi Eye Hospital, Aligarh, in 1967 and 1968. Pterygia removed from 45 patients were fixed, blocked, and sectioned, and stained with haematoxylin and eosin, van Gieson's stain, and Verhoeff's stain. Three showed typical "elastotic degeneration" and these tissues were subjected to enzyme digestion for periods of 1, 3, 6, 12, and 24 hours. The enzyme pancreatic elastase of 16 U/mg. activity* was used in 1 : 2000 dilution at 37°C (Sachar, Winter, Sicher, and Frankel, 1955). The diluent was 0·1 molar bicarbonate buffer of pH 8·6.

Microsections of goat aorta, which contains a large amount of elastic tissue, were used as controls.

Observations

(1) So-called elastotic degeneration (Fig. 1, overleaf) was seen in only three pterygia out of 45 cases (6 per cent.).

(2) The pterygium fibres showed no morphological change except for a little fading of the elastic stain (Fig. 2, overleaf).

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*Supplied by Calbiochem, Switzerland

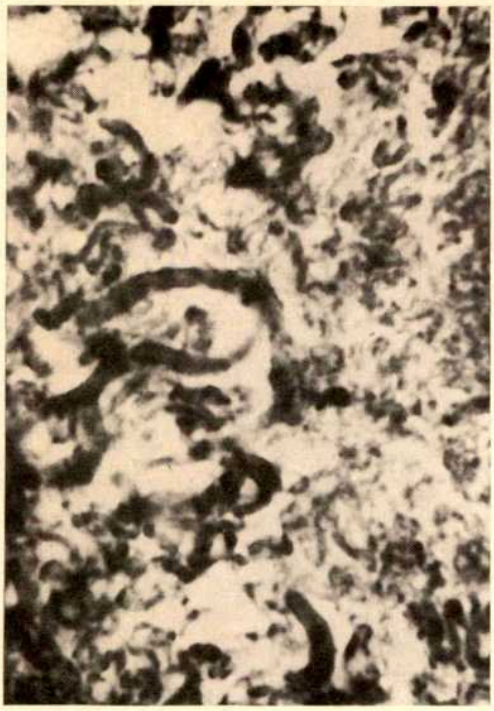

FIG. 1 *Photomicrograph of stroma of pterygium, showing elastotically degenerated collagen before enzymatic digestion, and vermiform degenerate fibres.* ×800

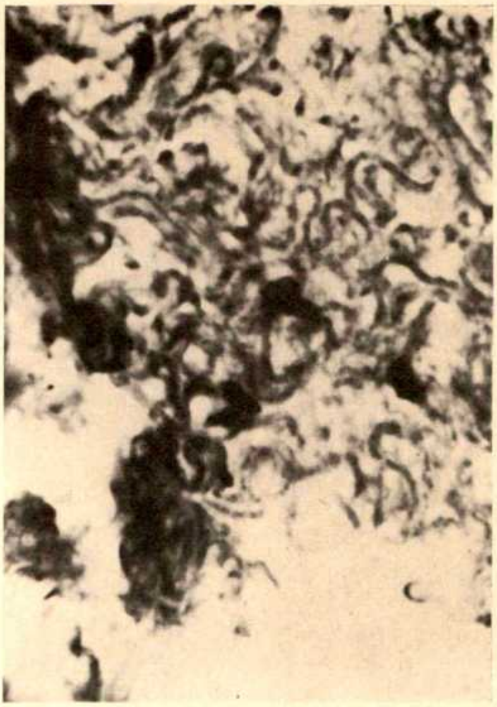

FIG. 2 *Stroma of pterygium, after 24 hours' enzymatic digestion by elastase, showing elastotically degenerated collagen, wtih some fading of Verhoeff's stain. The vermiform fibres show no morphological change.* ×450

(3) Elastic fibres of control goat aorta showed gradual splitting, granulation, and ultimately lysis under the influence of elastase (Figs 3 and 4).

Discussion

The routine staining reaction does not differentiate reliably between true elastic tissue and elastotically degenerated fibres (Gillman and others, 1954). Cogan and others (1959) therefore utilized the action of pancreatic elastase on the stromal fibres of pinguecula to determine their precise nature. Using as a control the elastic tissue of hog aorta, which contains much elastic tissue, they demonstrated that the controversial stromal fibres in a pingueculum did not seem to be real elastic tissue because they were only partially digested by elastase. They used the term "pseudoelastic tissue" for the fibres found in pinguecula.

The presence of similar fibres in the stroma of degenerating pterygium has been observed by all workers; Sugar (1949) and Sugar and Kobernick (1959) used the term "hyperelastosis" (an actual increase in elastic tissue), Gerundo (1951) wrote of "undulating fibres" and "an amorphous acellular mass with hyalinization" in various stages of a pterygium. Kamel (1954) could not go beyond "elastic tissue-like degeneration". Vass and Tapeszto (1964), in a histoenzymatic study of pancreatic elastase, concluded that the fibres were not true elastic tissue because they were only partially digested by elastase, and suggested that they were some form of altered collagen. These authors had used tissue from the human conjunctival fornix as a control. Duke-Elder (1965) called the process "elastotic degenera-

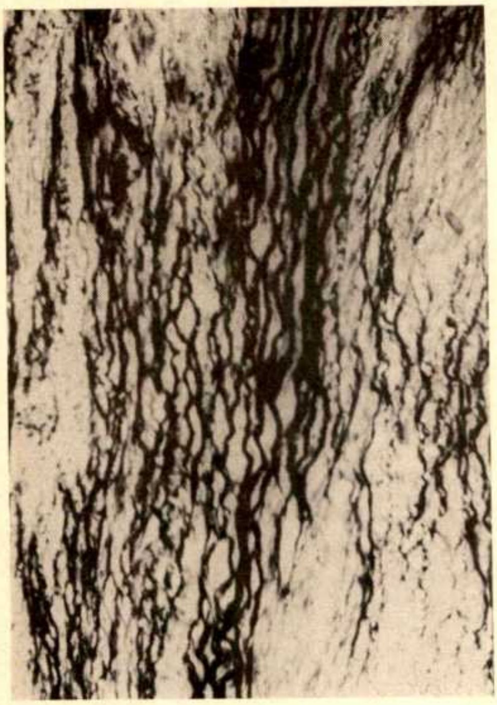

FIG. 3 *Photomicrograph of tissue from goat aorta, showing elastic tissue (black) before enzymatic digestion.* ×450

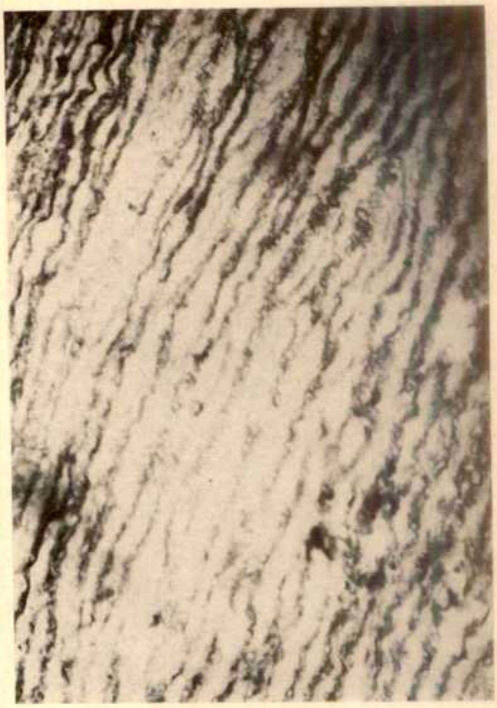

FIG. 4 *Tissue from goat aorta, after 24 hours' enzymatic digestion, showing swelling, granulation, and eroded appearance of elastic fibres.* ×450

tion" and attempted to close the controversy, but tradition dies hard. Cameron (1965) again mentioned "many-curled elastic fibres" and "wavy collagen fibres" replacing the superficial corneal lamellae, and wrote that "limbally the stroma of a pterygium showed a picture of senile elastosis". In a report on the histopathology of pterygium, Takebayashi (1966) referred to "increased elastic fibres".

In our series of 45 cases, the most important changes seemed to occur in the conjunctival stroma; 75 per cent. showed a hyperplasia of collagen, subconjunctival hyperaemia, and neovascularization. The hyperplasic collagen fibres showed fragmentation and a little coiling which we regard as a predegenerative stage. Clear-cut hyaline degeneration was seen in four cases and elastotic degeneration only in three in which the pterygium was of long duration. This late development of degeneration is an important feature distinguishing pterygia from pinguecula, in which the degenerative lesion is present from the beginning.

Our studies indicate that there is no hyperelastosis as was suggested by Sugar (1949) and Sugar and Kobernick (1959). The so-called elastic fibres are a degenerate form of collagen which takes up a misleading elastic stain. We therefore suggest the use of the term "pseudoelastic tissue" (Cogan and others, 1959). Moreover, judging from our material, this degeneration is not so common in pterygium as the literature would lead one to suppose.

The chemical basis of this altered staining reaction of degenerating collagen fibres is not known, though it has been shown that collagen and elastic fibres differ in the nature and amount of their amino acid content (Pearse, 1960). It is known that long-standing cultures of Gram-positive organisms become in time Gram-negative, probably through some change in the magnesium-ribonucleate content. This established phenomenon suggests that, as the collagen ages or degenerates in pathological conditions, it loses its natural staining character so that it can take up an elastic tissue stain. Since the staining depends mainly upon the surface chemicals, a degenerative product simulating one of the normal constituents of elastic tissue may perhaps be deposited in the area of degeneration. This might account for our observation that the enzyme elastase which could digest the true elastic tissue of aorta produced no morphological change in the area of degeneration in a pterygium apart from a little fading of the elastic stain.

Summary

45 pterygia were subjected to histopathological study by haematoxylin and eosin, von Gieson's stain, and Verhoeff's stain. The incidence of so-called elastotic degeneration was found to be low. The controversial convoluted fibres found in the stroma in three cases were studied with pancreatic elastase and were found to be "pseudoelastic" in nature.

Our thanks are due to Messrs. Calbiochem of Switzerland who supplied pancreatic elastase for this study, and to Mr. Khan, Technician in the Histopathology Department of the AMU Institute, for his help with the preparation of slides.

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Ocular fungus

Report of two cases

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Fungi are a large group of plant-like micro-organisms, which grow in filaments or "hyphae", and intertwine in a mat-like growth called a mycelium. Reproductive bodies or spores are produced from the colony or mycelium.

Ocular fungus was described by the early mycologists, including Leber (1879), who first reported the invasion of the cornea by *Aspergillus* causing hypopyon ulcer, and Gilchrist (1896), who described ocular involvement in blastomycosis. Ophthalmological research in fungus diseases began in the early 20th century, and interest has recently been renewed by discoveries in the field of antibiotic medicine and the development of cortisone and allied hormonal derivatives.

Hammeke and Ellis (1960) surveyed the fungi of the conjunctival sac, and in cultures from 520 eyes found fungi in 10·3 per cent. of adults, 5·0 per cent. of children, and 0·1 per cent. of infants. Williamson, Gordon, Wood, Dyer, and Yahya (1968) isolated fungi from 2·9 per cent. of healthy conjunctival sacs, and from 13·3 per cent. of patients with Sjögren's syndrome (the isolates included *Candida albicans* and *C. parapsilosis*).

The majority of fungus infections arise on the skin, which constantly receives debris from the air. Ringworm infections (tinea capitis, tinea barbae, tinea glabrosa, tinea cruris, and dermatophytosis) may involve the eyelids. Bedell (1946) reported a corneal ulcer due to cephalosporium (related to *Trichophyton gypseum*) successfully treated with potassium iodide.

Ocular blastomycosis frequently involves the lids, leading to scarring and distortion, with a liability to corneal ulceration. Theodorides and Koutrolikos (1953) reported four cases of blastomycosis of the conjunctiva. Schwartz (1931) described the only known case of metastatic infection reaching the eye from a generalized blastomycosis.

Streptothricosis conjunctivae (actinomycosis) commonly causes concretions in the canaliculi, and nodular granulations in the conjunctiva as well as corneal ulcers have been described. Actinomycosis is known to invade the orbit and eye from the sinuses and also from the jaw after dental extraction. Verhoeff (1924) reported the presence of actinomycosis after cataract extraction in both eyes, as well as by metastasis from an infection in which the fungus was isolated from the heart valves. Fuchs (1919) also found the fungus in enucleated eyes after cataract extraction.

Nocardia asteroides experimentally implanted in the eye by McCarthy, Kennedy, and Hazard (1959) caused granulomata and microabscesses similar to the conglomerate tubercle.

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Mycetoma (maduromycosis) begins with a subcutaneous swelling and forms a typical granulomatous lesion, which in India usually involves the foot, but two cases have been recorded in which the eyelids were affected (Aldridge and Kirk, 1940).

Sporotrichotic conjunctivitis was reported by Hamburger (1912) in 58 cases in which typical nodules broke down to form indurated ulcers. Toulant (1913) reported 23 ocular cases. McGrath and Singer (1952) found that salt-meadow hay harboured *S. schenckii*, which infected the palpebral conjunctiva.

Keratomycosis (moniliasis) usually follows trauma to the eye by an earthy substance, the mycotic corneal ulcer being covered by a dry membrane. Sykes (1946) reported a case of mycotic keratitis which appeared identical to dendritic keratitis and was treated by large doses of iodides, and by mycostatin locally and parenterally. Obstruction of the nasolacrimal duct is frequently due to *Candida albicans* (Birge, 1963).

Ocular involvement in coccidioidomycosis may occur in the form of conjunctivitis or proliferative retinitis in the initial stage of *C. immitis* infection (Levitt, 1948). Granulomatous uveitis was described at a later stage by Brown, Kellenberger, and Hudson (1958), who demonstrated endospores in the ciliary body and iris histologically, and observed others ophthalmoscopically in areas of choroido-retinitis.

Woods and Wahlen (1960) pointed out that benign histoplasmosis might cause granulomatous uveitis. In a survey of 293 patients with both granulomatous and non-granulomatous uveitis, they suggested that in the initial phase of benign infection, small granulomata appear at the periphery of the choroid. Haemorrhagic-oedematous lesions later appear at the fovea. These may be explained as hypersensitive reactions or atypical granulomata. Singer and Smith (1964) noticed lesions resembling phlyctenular keratitis and interstitial keratitis in the course of experimental histoplasmosis in rabbit eyes, after stromal injections of *Histoplasma capsulatum*; lesions resembling dendritic and disciform keratitis followed intra-epithelial inoculations.

Fleckner and Goldstein (1969) reported two cases of cerebral mucormycosis in diabetic patients, which were manifested by ptosis, proptosis, total ophthalmoplegia, loss of vision, and rhinitis.

Intraocular fungus infection may arise from a mycotic infection of the outer eye and adjacent tissues, or from a blood-borne infection from systemic disease (Duke-Elder and Perkins, 1966). Hammeke and Ellis (1960) reported cases of endophthalmitis in which fungi were isolated after surgery or trauma; of ten cases, five were saprophytes and five pathogens. Intraocular endogenous fungus infection has been recorded by Harley and Mishler (1959).

Case reports

Case 1, a girl aged 12 years, came to the out-patients clinic of the Ophthalmic Hospital at Tanta, complaining of sand particles in the left eye. The condition had started a month previously after she got sand in her left eye, and after 3 days the sand-like discharge increased in spite of washing out the conjunctival sac every half hour. The 'sand' increased during the night when the washings were stopped, and spilled out on to the left cheek. Terramycin eye ointment was given besides the frequent washings with cold water, but the condition still progressed.

Examination

The right eye was normal and the visual acuity 6/6.

The left eye showed a greyish-brown granular discharge like sand particles which filled the whole lower fornix and was spilling on to the lower lid (Figs 1 and 2). The eye was normal except for a mild conjunctival hyperaemia at the lower fornix. The fundus was normal and the visual acuity 6/12.

(1)

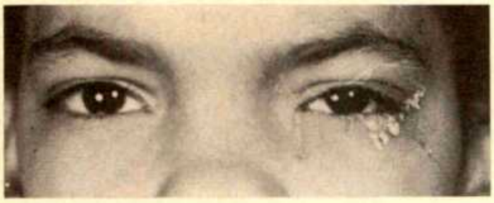

FIG. 1 *Case 1, showing fungus infection in the left conjunctival sac and on the lower lid*

(2)

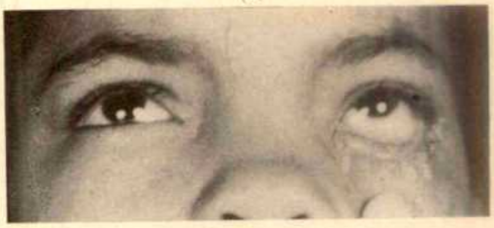

FIG. 2 *Case 1, showing fungus infection in the left lower fornix, and on the lower lid*

Bacteriological examination

Wet smears from the conjunctival discharge showed numerous broad septate branching hyphae (Fig. 3). A few dark spherical spores were also seen.

Cultures on Sabouraud's glucose agar medium incubated at room temperature showed growth starting on the third day in the form of a coal-black colony with solid dark spore heads (Fig. 4).

(3)

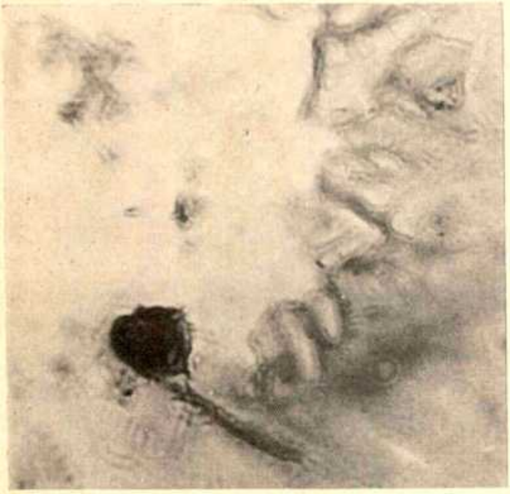

FIG. 3 *Wet smear with Gram stain from the conjunctival discharge, showing the hyphae, and a spore of* Aspergillus niger ×1,000. Oil immersion

(4)

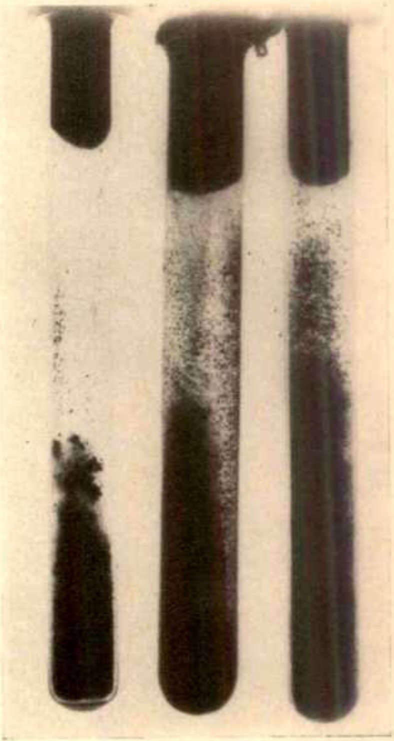

FIG. 4 *Cultures on Sabouraud glucose agar medium, showing* Aspergillus niger *colonies*

The spores were arranged in chains attached to sterigmata arising from the central vesicle (Fig. 5, overleaf). The cultures were typical of *Aspergillus niger*.

The right eye was also examined bacteriologically for fungus infection, but both wet preparations and cultures gave negative results.

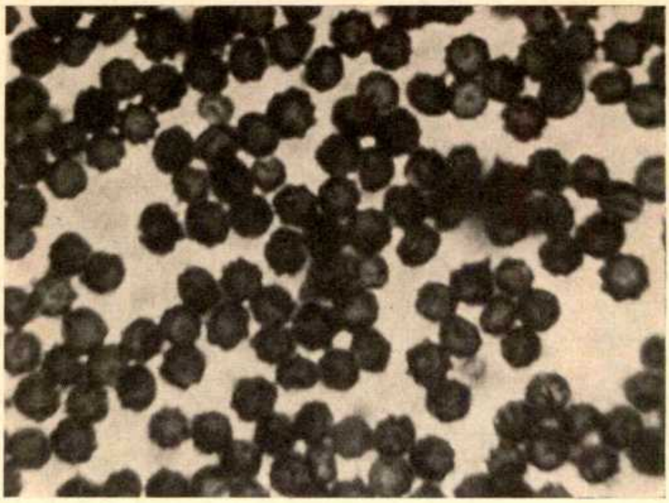

FIG. 5 *Culture on Sabouraud glucose agar medium, showing spores of* Aspergillus niger × 1,300. Oil immersion

Treatment

Mycostatin tablets (Nystatin), were prescribed in a dose of one tablet (500,000 units) orally three times daily for 2 weeks. The discharge was washed out thoroughly every hour and all local antibiotics were stopped. The condition continued to progress, however, and the discharge increased. Griseofulvin in a dose of one tablet (125 mg.) orally three times a day for 2 weeks was also ineffective, as were intramuscular injections of Sulpha-iode B (sulpha with iodine in organic form, with vitamin B_1) given every other day for ten injections.

Lastly, local mycostatin ointment (100,000 units Nystatin per g. in plastibase) was applied three times daily, and the condition responded completely after 5 days.

Case 2, a girl aged 13 years, came to the out-patients clinic of the Ophthalmic Hospital at Tanta, complaining of "mud growing" in the right eye. The condition had started gradually 2 months before, with a muddy discharge which progressively increased to fill the conjunctival sac, in spite of frequent washing with cold water. A vague history was given of dust particles entering the eye a week before the start of the discharge. The patient was using decadron eyedrops, and terramycin eye ointment, as well as the washing, but with no result.

Examination

The right eye showed a brownish-black discharge like mud at the lower fornix (Fig. 6). The lower lid was slightly oedematous, but the globe and fundus were normal, and the visual acuity was 6/12.

The left eye was normal with a normal fundus and the visual acuity was 6/18.

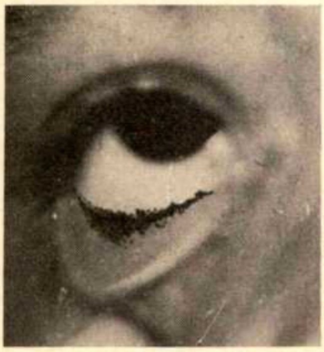

FIG. 6 *Case 2, showing fungus infection in the right lower fornix*

Bacteriological examination

Aspergillus niger was identified in the right conjunctival sac by wet smears and cultures on Sabouraud's medium. The appearances were similar to those in Case 1.

Treatment

The condition resolved after the application of local mycostatin ointment.

Discussion

The *Aspergillus* forms a very large group of easily isolated fungi. It is a rare cause of conjunctival infection, but corneal infections are more common, and the lacrimal passages and orbit may also be involved (Duke-Elder, 1965).

Aspergillus fumigatus has been identified as a cause of blepharitis (Rosenvold, 1942) and dacryocystitis; it has also been found to invade the cornea after 5 days' treatment of dendritic keratitis (Mitsui and Hanabusa, 1955).

An intractable and necrotic corneal ulcer is not uncommonly produced by the *Aspergillus*, particularly *A. fumigatus*, and a severe toxic iridocyclitis may result from the developing keratitis (Duke-Elder and Perkins, 1966). Perforating corneal ulcers have also been reported (Castroviejo and Muñoz Urra, 1921). The fungus may penetrate into the inner eye causing a vitreous abscess and panophthalmitis (Schirmer, 1896; Nobbe, 1898). Similar infections, which may be milder, have been reported after perforating injuries (Römer, 1902; Kampherstein, 1903; Purtscher, 1910; Rychener, 1933; Watelet, 1950).

Aspergillus niger was reported by Donahue (1949) in a 12-year-old girl: a brownish-black swelling containing a treacle-like fluid was found in the conjunctiva and inferior canaliculi.

Aspergillus can easily be identified by the examination of wet smears for broad, septate, branching hyphae. Small dark spherical spores, 2 to 3 μ in diameter, may sometimes be seen. Cultures on Sabouraud's glucose agar or Littman's ox-gall agar incubated at room temperature show a rapid growth (within 2 to 3 days), beginning as a fine filamentous surface growth and producing conidiophores. The *Aspergillus* is characterized by the swollen ends of the conidiophore called sterigmata, from the tips of which the spores arise in long chains. The colour of the colony depends on the species. *Aspergillus niger* produces a coal-black spore head (Moss and McQuown, 1960).

Fungi can be diagnosed macroscopically by the characteristic colony formation and the fusion of their mycelia, and microscopically by the type of spore. The recognition of the arrangement of the spores is essential for identification of the species. Conjunctival smears and biopsy material, together with mucous plugs from the tear ducts, may be examined directly under the microscope (Birge, 1963). The pathogenic fungi all form hyphae, or irregularly segmented filaments, in the human body; whereas spores are rarely present except in artificial culture.

Most fungi are demonstrated with ordinary histological stains such as haematoxylin and eosin; but Gram, periodic acid-Schiff, and silver stains are usually more effective. If tissue is available, the PAS staining technique readily reveals the morphological characteristics of many fungi (McManus, 1948). For photo-micrographic work, Gomori's methenamine silver nitrate technique has been recommended.

Fungus culture media, like Sabouraud's glucose agar medium, make the growth and identification of fungi more specific. It is important to inhibit bacterial growth in routine cultures, and Sabouraud's media do this by their acid pH (5·5) and also by their high sugar content (Hynes, 1964). Filtered ultraviolet irradiation may be used to assist the study of fungus colonies (Birge, 1963).

Immunological procedures are also available for certain fungi, but the complex antigenic structure of most of them makes the interpretation of such tests difficult (Conant, Smith, Baker, Callaway, and Martin, 1954). Skin hypersensitivity tests performed by the intracutaneous injection of the antigen are available for *Mucor*, *Aspergillus*, *Candida*, and *Histoplasma*, but the positive results tend to appear late in the course of the infection (Duke-Elder and Perkins, 1966). Animal inoculation may be used, especially with deep mycotic infections, to establish the pathogenicity or to obtain a pure strain. Agglutination and precipitation tests are also available for histoplasmosis (Saslaw and Campbell, 1948; Salvin and Hottle, 1948).

The treatment of oculomycosis is unsatisfactory. Most cases are not precisely diagnosed to begin with, so that intensive broad-spectrum antibiotics and steroids are usually administered as a routine measure. Most fungi thrive in the presence of antibiotics, particularly streptomycin and the tetracyclines (Duke-Elder and Perkins, 1966). Torack (1957) reported thirteen cases of fungus infection associated with antibiotic and steroid therapy, and Mitsui and Hanabusa (1955) found that patients treated with corticosteroids for 3 weeks had a 49 per cent. greater chance of fungus invasion than those not so treated. Ley (1956) has also shown the enhancing effect of corticosteroids in fungal infections of the cornea in experimental animals.

The most effective fungistatic agents are mycostatin, amphotericin B, and griseofulvin. Experimental intraocular infection with *Aspergillus fumigatus* in rabbits (Fine and Zimmerman, 1960), proved that mycostatin, derived from *Streptomyces noursei* (200 units in 0·1 ml. saline solution), controlled the intraocular infection completely after 7 weeks; the best results were obtained when treatment was started 24 to 48 hours after the infection. Hammeke and Ellis (1960) advised the use of prophylactic pre-operative local antifungoidal drugs, such as amphotericin or nystatin.

Summary

Two cases of conjunctival *Aspergillus niger* infection are reported. A dramatic response was obtained by the local use of mycostatin ointment.

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Effect of channelling on hydrostatic pressure behind a haptic lens

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The fluid beneath a well-fitting haptic lens with no channel or fenestration is believed to remain perfectly sealed off. This is known to lead to the corneal surface being deprived of oxygen with consequent oedema and clouding (Smelser, 1952; Kinsey, 1952). A contributory cause for the corneal distress may be the development of a negative pressure under the lens; this appears to be present since many such lenses appear to cling to the eye and resist removal.

The purpose of the experiments described here was to determine the fluid pressure behind a flush-fitting lens and its variation with eye movements, and to see how it was affected by channelling.

The tests were of a preliminary nature and were carried out on one subject only.

Methods

A hydrogel impression of the eye was taken, and a stone cast made from it. A 0·6-mm.-thick shell moulded from Acrylic‡ was fitted to make contact over at least half the corneal surface and was hand-worked to give a transition with limbal clearance (Ruben, 1967). This lens is denoted A; an identical shell A_1 was prepared with an inferior-nasal channel. Three other shells, B, B_1, and B_2, were also fabricated with none, one, and two channels respectively. These were similar to A, but had a central back optic 0·6 flatter than K (K = 7·8 H) polished onto this surface and the haptic settled back until corneal contact was achieved.

A small hole was drilled in these shells at the limbal transition zone into which was cemented a short length of polyethylene tubing§ which connected the fluid to the manometer. This tubing was cold-stretched over a few cm. near its connection to the lens in order to increase its flexibility. The hydrostatic pressure was measured with a Sanborn pressure transducer which was prepared as described by Hedbys, Mishima, and Maurice (1963) to approach the volume displacement of 0·05 mm.^{3}/100 mm. Hg claimed by the manufacturers. No attention was paid to temperature control of the system owing to the less stringent conditions of operation.

To conduct an experiment the manometer was adjusted so that the lens could be placed in a suitable position with the connecting tube exerting the least possible traction upon it. The shell was turned face down and filled with saline, and the recording manometer set to zero pressure. An index mark was made on a vertical mirror at the level of the saline meniscus, so that the subject by observing his own eye opposite this mark would ensure that no differences in fluid level were introduced into the recording system. The true hydrostatic pressure behind the lens could then be read directly from the manometer recording. Before the experiment the calibration was established by altering the height of the saline-filled contact lens shell from its zero position by definite amounts. The baseline was checked for drift at the end of each run.

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‡Imperial Chemical Industries, polymethacrylate C.Q I.
§Portex polyethylene tubing No 270

When the equipment was prepared, the lens was inserted into the eye and allowed to settle with the eye looking forward. When the pressure had become established the eye was rotated, either slowly or quickly, as far as its extreme positions.

The correct operation of the system could be checked by the subject raising and lowering his head by a few cm. from the zero position when appropriate deflections of the recorder occurred.

Results

With the eye in the primary position, a negative pressure behind the lens was immediately developed and was maintained. Its magnitude was generally between 2 and 3 cm. H_2O, regardless of whether the lens was channelled or not.

Movements of the eye either had no effect or increased the suction. The changes were never more than 10 cm. H_2O initially and lessened gradually if the position was maintained. In this subject, nasally directed movements produced the greatest effect. Slower movements appeared to cause lesser changes, and channelling tended to diminish the responses slightly. The pressure never became zero or positive on returning to the forward direction.

Blinking caused a sharp excursion of variable extent and in either direction. Forcible closure of the lids was also variable in its effects, but generally tended to increase the suction behind the lens. The recordings are shown in the Figure.

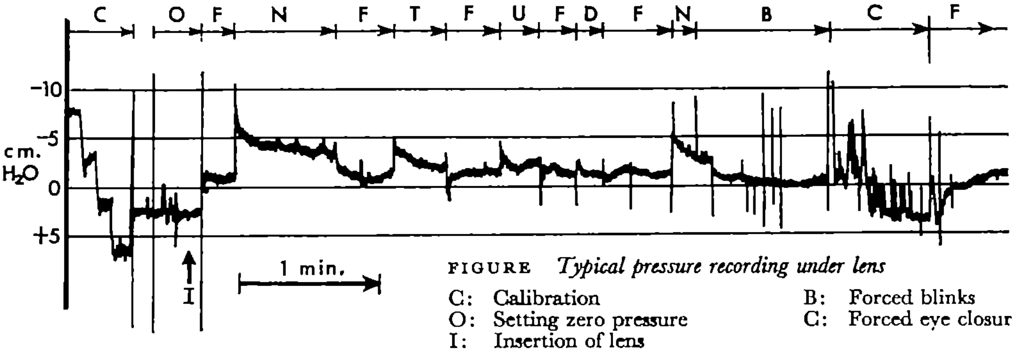

FIGURE *Typical pressure recording under lens*

C: Calibration
B: Forced blinks
O: Setting zero pressure
C: Forced eye closure
I: Insertion of lens
F: N: T: U: D: Eye looking forward, nasally, temporally, up, down

Discussion

Though the lenses appeared to be an acceptable fit and their behaviour may well be representative of similar well-fitted lenses, the results should be accepted with caution since they were derived from a single subject. It appears that the suction beneath the lens never becomes strong enough to be of significance in the mechanical stability of the epithelium, bearing in mind that the hydrostatic pressure in the stroma on the other face of the cellular membrane is of the order of −50 cm. H_2O in the normal cornea (Hedbys and others, 1963).

It may also be noted that channelling appears to have no marked effect upon this pressure, so that any benefit it confers is likely to be only by way of increasing the circulation of tear fluid under the lens and hence the access of oxygen to the cornea.

We should like to thank Miss Anna van der Ham who was the subject in these tests.

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Fluid exchange under scleral contact lenses in relation to wearing time

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Scleral contact lenses are extensively prescribed in certain centres, especially when the eyes to be fitted are abnormal. The original sealed lens prevented the tear fluid behind it from exchanging with the lacrimal secretion present in the conjunctival sac. In consequence, the corneal epithelium rapidly became depleted of oxygen, and this resulted after a few hours in the misting of vision and the appearance of haloes (Smelser, 1952).

In order to promote the circulation of the fluid over the cornea, scleral lenses have been designed with fenestrations or with channels. There appear, however, to have been no objective tests of the effectiveness of these procedures. One way to ascertain this is to stain the fluid behind the lens with fluorescein and to measure the rate at which the fluorescence is lost; this rate of loss should represent the rate at which unstained tear secretion replaces the original fluorescein-stained fluid. Fluorescein was used for this purpose in the pioneer experiments of Smelser (1952), but a specially designed lens had to be made to collect the dye for measurement at the end of a test, and repeated tests were required to determine the rate of loss.

The availability of the slit-lamp fluorophotometer designed by one of us (Maurice, 1963) has made it possible to follow accurately the changes in dye concentration behind a normal lens during a single wearing period.

Method

Patients who had been routinely fitted with scleral lenses at the Contact Lens and Prosthetics Department of Moorfields Eye Hospital, High Holborn, were used as subjects for these tests. Three patients (four eyes) wore fenestrated lenses (F) and eight patients (ten eyes) channelled lenses (C). The channels were grooves in the haptic from the zones of corneal clearance to the periphery of the lens. The fenestration was 1 to 1·5 mm. in the limbal clearance zone and was usually sited temporally. The maximum continuous wearing time without misting of vision was noted for each patient. The nature of the test was explained and the lens inserted on to the eye to be tested. Physiological saline buffered to pH 7·2 and warmed to body temperature was used as insertion fluid. A baseline measurement resulting from scattered light and natural fluorescence was made at a point of contact lens clearance from the cornea. The patient then removed the contact lens, filled it with a solution of 10^{-6} g./ml. fluorescein in physiological saline (pH 7·2), and then re-inserted it.

The patient had previously become accustomed to being observed through the fluorophotometer. The clearance zone behind the lens where measurements could be conveniently carried out was identified as quickly as possible, and readings were made at suitable intervals for a period of an hour or more. Between measurements the patient was allowed normal freedom of movement. At the end of the test the lens was removed, filled with an unstained saline solution, and re-inserted. This allowed a baseline reading to be taken from the same point under the contact lens.

Since most of the lenses were closely fitted apically, the smallest sensitive window of the fluorophotometer (approximately 0·075 mm. wide) had to be employed, and a search had frequently to

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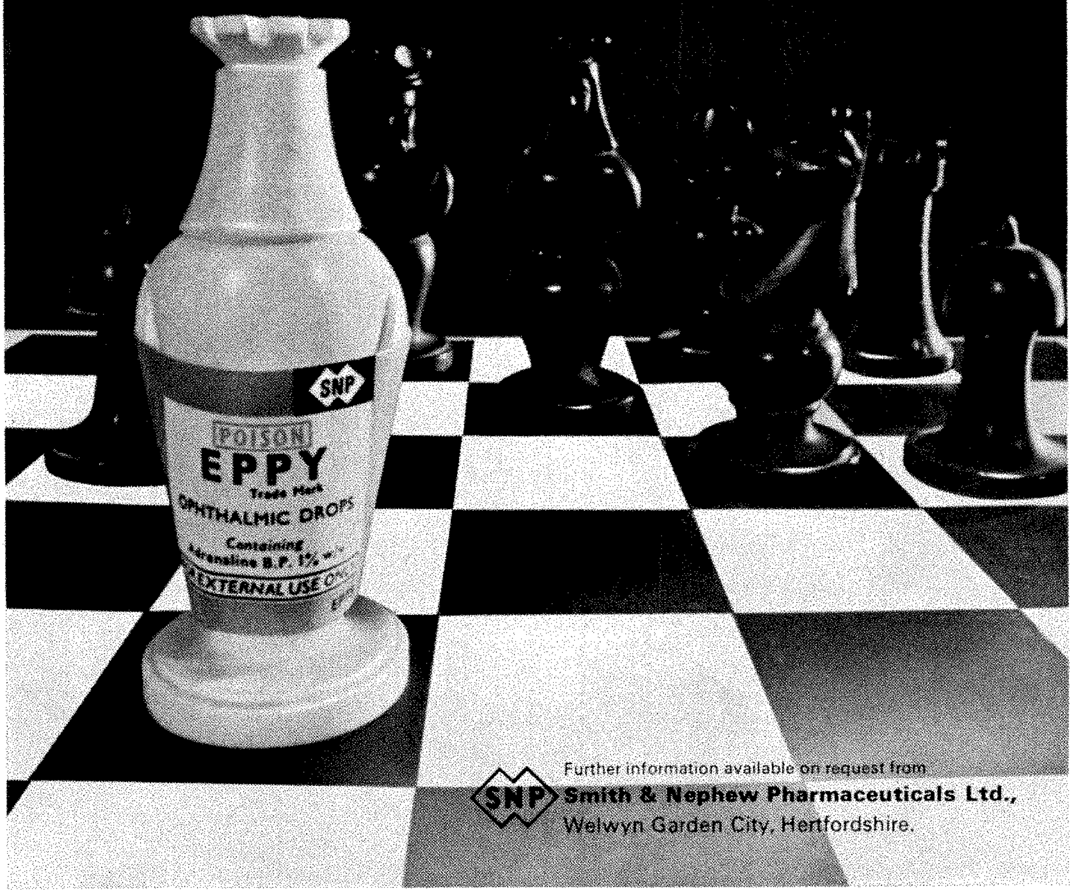

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be made to find a region where the lens was sufficiently separated from the corneal surface for the sensitive area to lie entirely within the image of the illuminated slit of fluorescent liquid. Once this was found, the patient could be encouraged to direct his gaze in the appropriate direction during measurements and with experience little difficulty was encountered in obtaining consistent readings.

No unequal mixing of the fluorescent fluid behind the lens, or staining of the cornea, was macroscopically observable in these tests.

Results

The readings, corrected by the subtraction of the baseline value, were plotted against time on semilogarithmic paper. As would be expected, the points tended to fall on a straight line, and from this the decay of the fluorescence could readily be derived to a sufficient degree of accuracy. The decay was expressed by an exponential coefficient which corresponded to the proportion of the fluid behind the lens which was replaced in a given time interval.

This coefficient varied enormously between different subjects. Fig. 1 illustrates the results from F1, the patient with the highest values, whose left lens had an exchange coefficient of about 12 per hour, indicating that the fluid behind it was replaced every 5 minutes.

By contrast, Fig. 2 shows the results in C7, a patient in whom the coefficient was only about 0·3 per hour, so that only 30 per cent. of the volume of fluid was exchanged in a

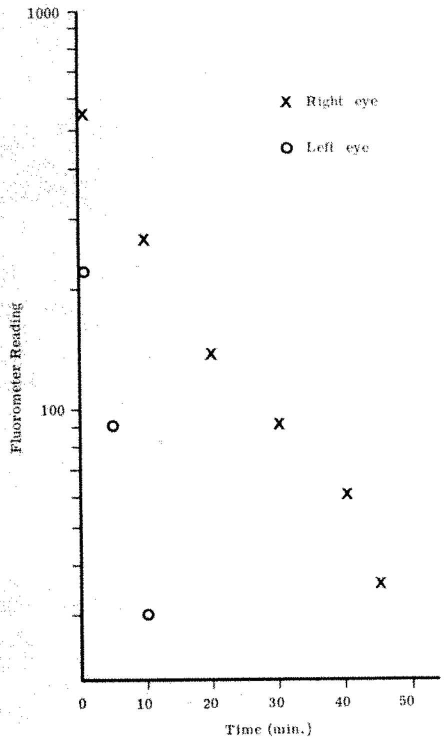

FIG. 1 *Decline in fluorescence behind lenses of patient F1 (fenestrated lenses)*

Ordinate: Fluorometer reading (arbitrary units)

Abscissa: Time after insertion of lens

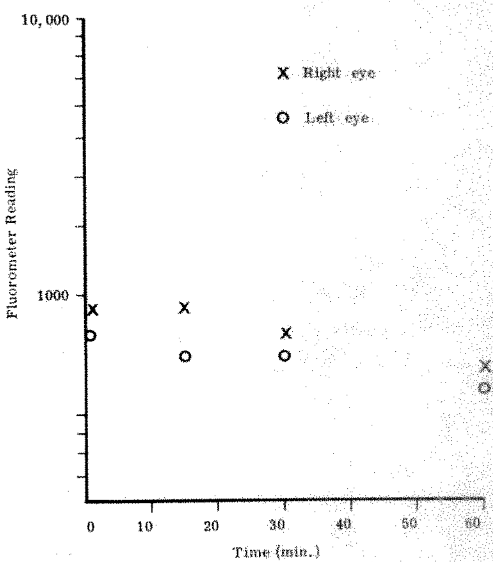

FIG. 2 *Decline in fluorescence behind lenses of patient C7 (channelled lenses)*

one-hour period. Two extreme cases demonstrated no appreciable decline in fluorescence over a period of more than one hour, indicating that the lenses were effectively sealed although the channels were functional by clinical tests.

The results obtained from all eleven patients are summarized in the Table where the exchange coefficients are compared with the reported wearing times.

Table *Fluorescein exchange rates and wearing times for patients with fenestrated* (F) *or channelled* (*C*) *lenses*

Lenses	*Patient no.*		*Exchange coefficient* (1 *hr*)	*Wearing time* (*hrs*)
Fenestrated	F1	RE	3·5	16
		LE	12·0	16
	F2		1·2	4
	F3		2·3	4
Channelled	C1		1·8	5
	C2		1·4	5
	C3		0·5	10
	C4	RE	0·7	5
		LE	1·6	4
	C5		2·3	2
	C6		3·4	4
	C7	RE	0·2	3–4
		LE	3·4	3–4
	C8		0·2	3–4

Discussion

The oxygen uptake from the air over the total surface of the human cornea has been measured to be about 6 μl./hr under normal conditions (Hill and Fatt, 1964). There are no direct experiments to determine what is the smallest uptake required to save the cornea from metabolic embarrassment. The calculations of Fatt, Bieber, and Pye (1969), though beset with assumptions, would suggest that the uptake could drop to 4 μl./hr, 4 = ⅔ of the 6 given above before the oxygen consumption of the tissue was restricted, and that at no point would it be entirely suffocated, even if the uptake were as little as 0·6 μl./hr, ten times less than 6.

If the cornea is closed off by a lens, the gas can be brought to its surface only when dissolved in the tear fluid which exchanges with the trapped volume of fluid. Given the solubility of oxygen (0·5 vol. O_2 in 100 vol. H_2O at 37°C.), it seems probable that somewhere in the region of 100–1,000 μl./hr of fresh tear fluid should replace that under the lens in order to satisfy the minimal respiratory demands of the cornea.

It should be emphasized that the exchange coefficients displayed in the Table show only what proportion of the fluid behind the lens is exchanged in an hour. To estimate the rate of fluid exchange the actual trapped volume must be known. Thus if we assume the overall clearance to be 0·5 mm., the trapped volume will be about 70 μl. Then the fastest exchange rate (Fig. 1) will correspond to a tear movement under the lens of 840 μl./hr and the slow rate (Fig. 2) to one of 20 μl./hr. Put another way, an exchange coefficient of 13 per hr should correspond to complete satisfaction of the corneal requirements and one of 1·3 per hr to effective suffocation. Intermediate values might lead to the appearance of visual disturbances after a delay.

Although the actual trapped volumes are uncertain in individual cases, the results shown in the Table are generally explicable from this point of view. Apart from patient F1 only one other (C3) had a wearing time greater than 5 hrs. These wearing times do not indicate the limit of tolerance but the onset of misting of vision and superficial corneal oedema. Experienced wearers are known to achieve times as long as this even with totally sealed lenses. The conclusion may be drawn, therefore, that the fenestration was totally achieving its purpose only in patient F1. Channelling was probably helping none of these patients in respect of oxygen replacement.

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Late results of cerclage operation for retinal detachment

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Developments in the surgery of retinal detachment since the time of Gonin have led from simple to more complicated methods which are not always more effective.

Among the simple methods is the cerclage operation, developed by Arruga, in which a string of Supramid thread is sewn around the eyeball on the sclera and a sharp buckle is created, thus diminishing the volume of the eye and separating the region of the holes from the healthy area of the retina.

In our department we have modified the Arruga method by using two parallel strings of Supramid sutures. They are applied after the holes have been treated with diathermy, thus achieving a more complete separation of the region of the holes from the central and peripheral areas. The holes lie between the two sutures which create a buckle which protrudes into the eye with the holes lying on the crest of the buckle.

The Figure shows the difference between the single-string and double-string methods. The single string separates the region of holes from the central part of the retina and our double strings separate the holes both from the central part of the retina and from the periphery.

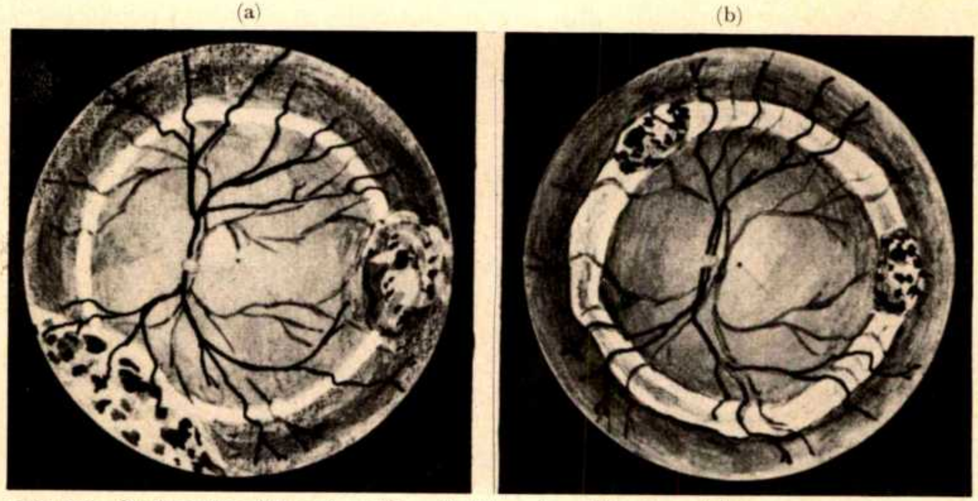

FIGURE *Single cerclage (Arruga) on left. Double cerclage (Hauer) on right*

The Arruga operation is simple and does not take long to perform, and the results are as good as those of more complicated methods. Its chief disadvantage is that the suture may penetrate the sclera and enter the vitreous, thus causing a total nonoperable detachment. In the series described below this happened in only one case, that of a patient with blue sclera. Another disadvantage is the anterior segment necrosis that may follow all kinds of encircling procedures.

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Present investigations

The late results of 34 cerclage operations performed in our department during the years 1962–1967 are reported in this paper. We performed the Arruga operation according to the original method in eleven cases, and used our modification in 23 complicated cases involving giant holes, multiple holes in many quadrants, or vitreous retraction. This series does not include cases without retinal tears or cases with a macular hole.

CLINICAL PARTICULARS

Most of our patients had been operated on during the first 3 years (1962 to 64) but as our enthusiasm for this type of operation waned, the number of operations diminished accordingly.

In nineteen cases this was performed as a first operation, in ten as a second, and in five as a third.

In twenty of our cases the holes were concentrated in only one quadrant, in eleven cases in two, and in three cases in three.

Most of the tears or holes were concentrated in the upper temporal quadrant (19 cases), and the smallest number was found in the lower nasal quadrant (7 cases). The two other quadrants were equally affected (13 cases).

Sixteen of our 34 were myopic and there were ten cases of aphakia.

Results

ANATOMICAL

In 28 out of 34 cases (82·3 per cent.) a permanent reattachment was achieved.

FUNCTIONAL

In five cases the visual acuity was between 6/6 and 6/10, in ten between 6/12 and 6/30, and in thirteen between 6/60 and 3/60.

In six cases the retina did not become reattached and blindness ensured.

In one case the string penetrated the eyeball, in three the operation was complicated by anterior segment necrosis, in one there was a massive vitreous retraction, and in the last there was a very old detachment with fixed folds.

Summary

The Arruga method of cerclage operation has been modified in our department by using two encircling Supramid sutures instead of a single one in order to isolate the region of holes from both the central and the peripheral parts of the retina.

Although many new methods of operation for retinal detachment have been developed, the postoperative results of the simple cerclage method are no worse than those of the newer methods from the functional and anatomical points of view.

In 34 cerclage operations carried out in our department from 1962 to 1967 in cases of severe retinal detachment, giant holes, multiple holes, and vitreous retraction, good results with full reattachment of the retina were obtained in 28 (82·3 per cent.)

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Autoextraction of superficial corneal foreign bodies

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It is not uncommon for foreign bodies such as dust and coal particles to enter the eye when no medical facilities are available. Because of its exposed position, the cornea is more vulnerable than the conjunctiva and over three-quarters of retained surface foreign bodies lodge on the cornea (Roper-Hall, 1964).

Conjunctival foreign bodies on the bulbar conjunctiva or in the lower fornix or the sulcus subtarsalis present little difficulty, but the cornea is too sensitive to be touched without a local anaesthetic, and the eye should not be rubbed to relieve irritation. By the following simple method the patient may be able to remove a foreign body himself.

Method

The eye should be gently closed. The centre of the skin of the upper lid should be held above the lid margin between the thumb and index finger (Figs 1 and 2), jerked abruptly away from the eye (Fig. 3), and then released. The separation of the lid from the eyeball makes a slight noise like smacking the lips. This process may be repeated three or four times. The patient should move the upper lid to feel for the foreign body sensation, the absence of which will indicate that the gritty particle has been successfully dislodged from the cornea. The eye may afterwards be irrigated with clean tap water.

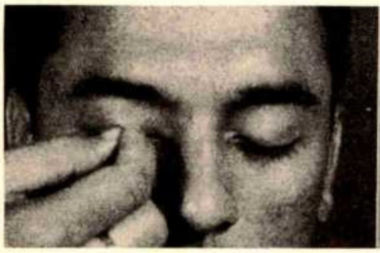

FIG. 1 *Front view, showing skin of upper lid held between thumb and index finger*

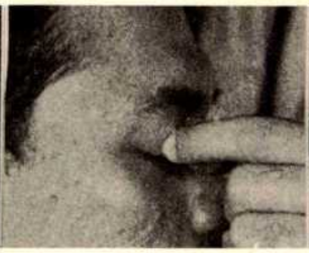

FIG. 2 *Side view of Fig. 1*

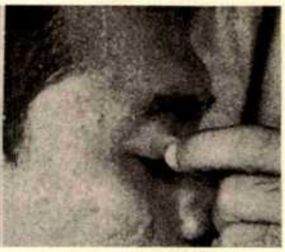

FIG. 3 *Side view, showing skin of upper lid pulled forwards*

Discussion

When the eye is gently closed the conjunctival space filled with tears forms a closed cavity (Duke-Elder, 1961). As the upper lid skin is pulled away from the cornea, a vacuum is created with a sucking effect which is strong enough to draw a superficial foreign body away from the cornea.

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This method may be used as a routine first aid measure in all cases of corneal foreign bodies, as it will not damage the cornea and does not require a local anaesthetic.

The patient must keep the eye closed in order to create a vacuum, and the skin must be pulled suddenly so that the sucking or smacking sound is produced.

Summary

A simple technique for the autoextraction of superficial corneal foreign bodies is described. It may be attempted as a first-aid measure for the extraction of all corneal foreign bodies.

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The last needs a special instrument for its application and a suitable type of forceps is described here. The tube has an internal diameter of 0·03 in. and an external diameter of 0·06 in., and thus a spreading forceps with extra fine points is required.

A simple substitute for the costly cross-action forceps can be made from a fine mosquito forceps by filing the points to one-third their normal thickness ½ in. along their length (Fig. 1).

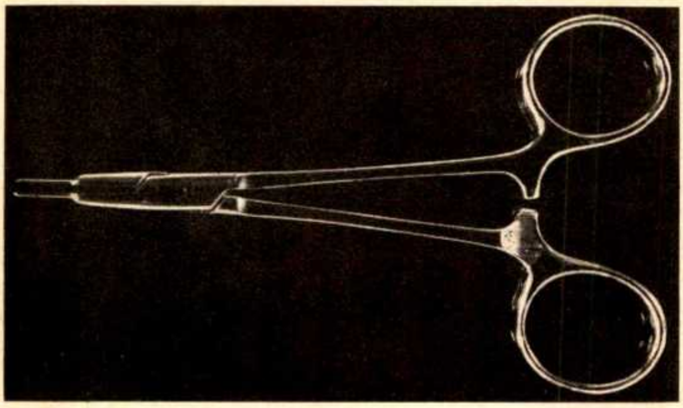

FIG. 1 *Fine forceps with points filed very thin*

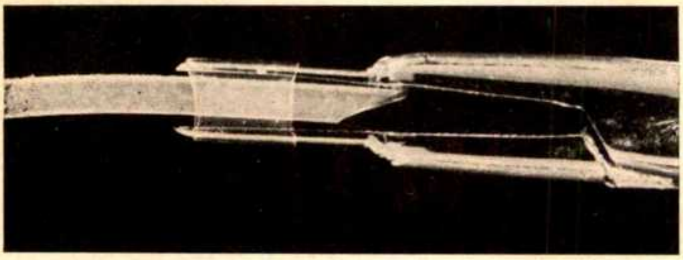

FIG. 2 *Feeding the band through the sheath while it is held open by the finely pointed forceps*

With the tube fitted over the tips and the points spread, the band can be fed through the sheath (Fig. 2); sharpening the ends of the band makes this manoeuvre easier. The final position is shown in Fig. 3 (opposite).

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* Supplied by the Dow Corning Co., Ltd

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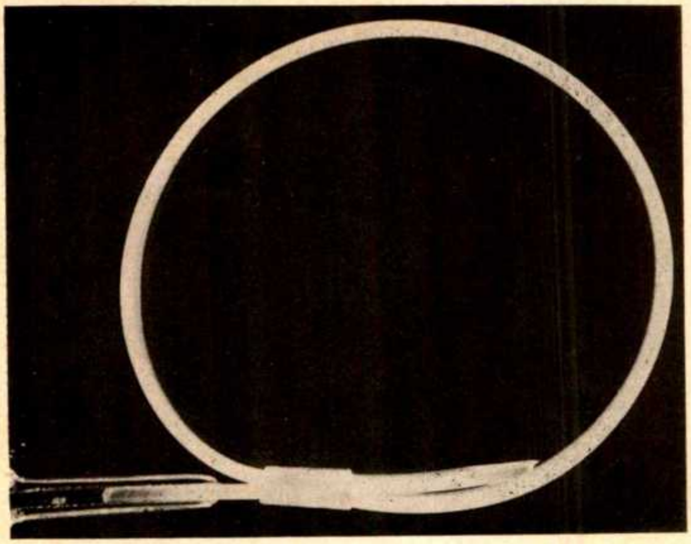

FIG. 3 *The ends of the encircling band held together by the sheath*

Brit. J. Ophthal. (1970) **54,** 496

Fixation problems in fundus photography

S. S. HAYREH* AND T. J. FFYTCHE
Institute of Ophthalmology, University of London

All those who use the West German Zeiss fundus camera (Fig. 1) for routine fundus photography or fluorescence fundus angiography may be confronted with the following problems while using the conventional fixation target outside the camera:

(**1**) The conventional external target is of no use for subjects with a single functioning eye, with the other eye either excised or blind or with no fixation.

(**2**) It may not be possible to photograph areas temporal to the optic disc in patients who converge on looking at the target at near distance.

(**3**) It is not possible with the conventional external target to photograph areas temporal to the macular region without good co-operation from an intelligent patient. This is because the movement of the external target is obstructed by the tube of the camera.

(**4**) It is difficult for patients with markedly constricted tubular fields or defective dark adaptation to follow the movements of the external target.

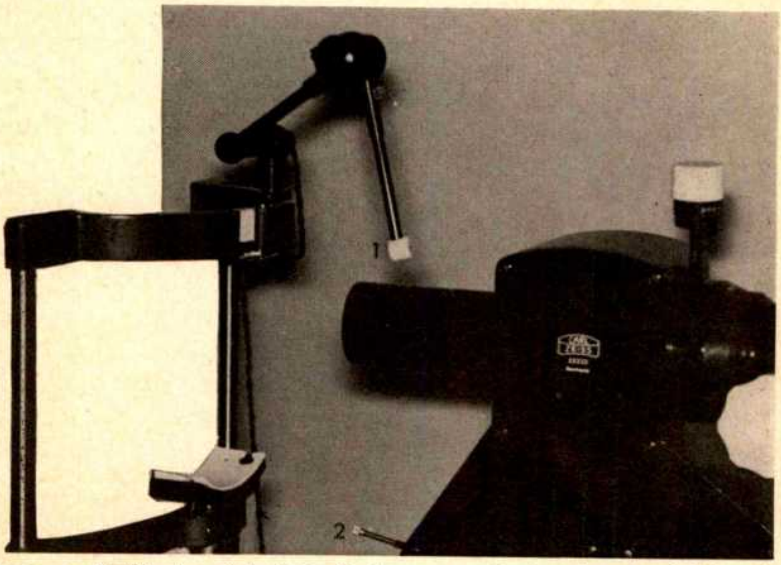

FIG. 1 *Profile view of the Zeiss fundus camera, showing the external* (1) *and internal* (2) *fixation targets*

With these problems in mind, we have used the fixation target provided inside the camera (Figs 1 and 2), which has proved extremely helpful in these difficult cases. The patients have found it very convenient to focus on the target and follow it. It has been possible to photograph, not only the macular area, but also the regions around it extending nasal to the optic disc and temporal to the macular area, as well as above and below the macular

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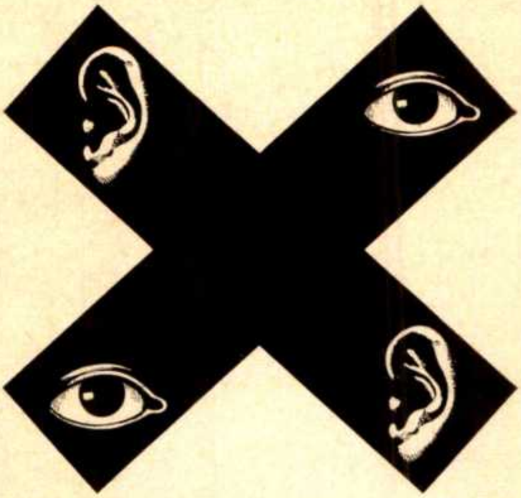

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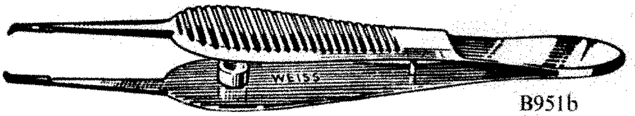

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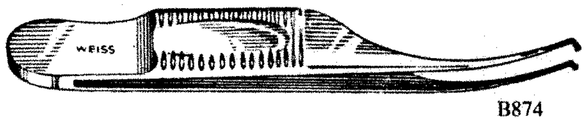

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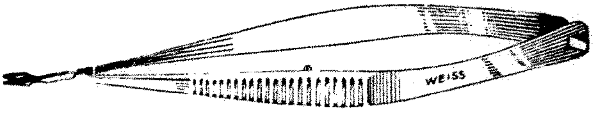
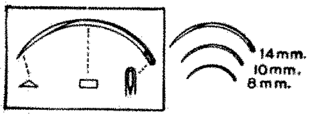


B1053

B951b. **Suture Forceps,** corneal, St. Martin's, *stainless steel.*
B874. **Forceps,** corneal, Barraquer's *do.*
B1053. **Scissors,** miniature, for removal of corneal sutures, etc.



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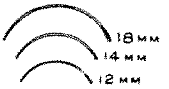

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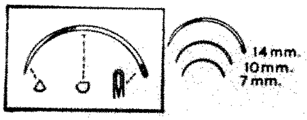

B609

B607. **Needles** corneal, Jameson Evans', 8, 10 and 14 mm.
B608. Ditto do. Kalt's, 12, 14 and 18 mm.
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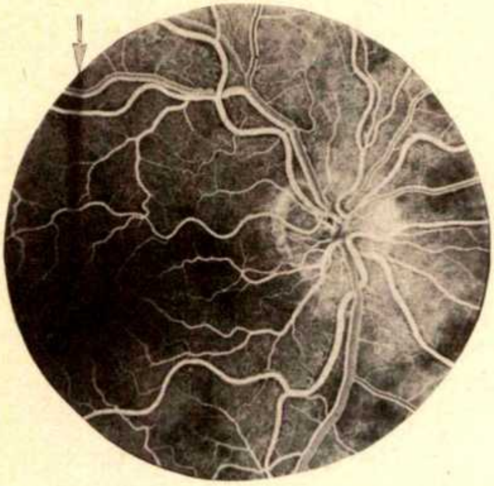
region. Most of the posterior pole can be covered by this means, and it is also possible to assess the point of fixation in patients with macular lesions (Fig. 3).

(2)



(3)

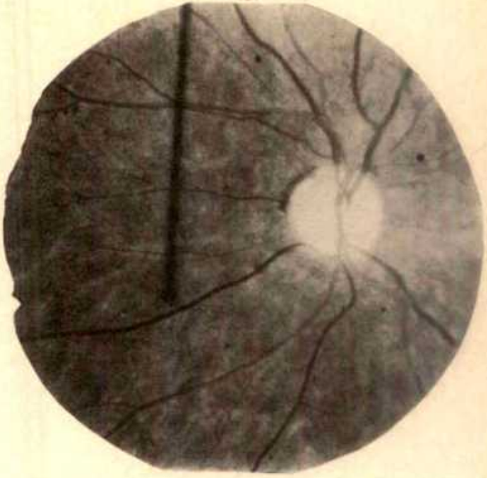


FIG. 2 *Fluorescence fundus angiogram, showing the internal fixation target* (*arrow*)

FIG. 3 *Fundus photograph, showing eccentric fixation in a patient with extensive pigmentary degeneration and loss of macular fixation in both eyes*

We are grateful to the Audio-Visual Communications Department of the Institute of Ophthalmology for the photographs.

Brit. J. Ophthal. (1970) **54**, 498

Treatment of corneal rust rings with desferrioxamine

P. J. NORTH

The Royal Berkshire Hospital, Reading

Desferrioxamine (Desferal, CIBA) eyedrops have been used for a number of ocular lesions caused by iron-containing compounds (Galin, Harris, and Papariello, 1965; Wise, 1966; Valvo, 1967; McGuinness and Knight-Jones, 1968). This paper describes the results of treating 36 patients with rust staining of the cornea and a complication possibly due to this drug which has not previously been described.

Clinical observations

In this series, treatment was confined to corneal rust rings (after surgical removal of the original foreign body if necessary). The patient was prescribed gutt. desferrioxamine four times a day and reviewed regularly. The results were as follows:

Rust removed	27
Rust remaining, no symptoms	4
Rust remaining, with symptoms (after 7 days treatment)	2
Other	3
Total	36

The two patients with remaining rust and symptoms had the rust surgically removed and became symptom-free.

In the last group, one patient complained of continued irritation in the eye for which no cause could be found. The other two patients developed corneal ulceration in the area of the original foreign body; although at this time there was no remaining rust, there was a heavy flare and cells in the aqueous. Both were treated with gutt. atropine 1 per cent., an antibiotic ointment, and padding. The ulceration healed in both cases within 3 days.

Discussion

No cases of reactions to desferrioxamine given locally have previously been reported. Two patients in this series developed corneal ulceration, which settled quickly, leaving no visual disability. There were no cases of allergy. Further observations are required to determine whether there is a true causative relationship.

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McGuinness and Knight-Jones (1968) have reported that there is no significant difference in efficacy between surgical and medical removal. However, desferrioxamine presents two advantages:

(1) With the wider geographical spacing of ophthalmic units in the periphery, many non-ophthalmologists would be competent to remove the original foreign body and treat remaining rust with desferrioxamine, thus saving many patients a long journey.

(2) If the drops can be instilled into the eye of a young child, the use of general anaesthesia may be avoided.

My thanks are due to Mr. G. T. W. Cashell, Mr. E. W. Dorrell, and Mr. J. McMillan for permission to report cases under their care, and to Dr. D. M. Burley of CIBA Laboratories for supplies of gutt. desferrioxamine.

References

GALIN, M. A., HARRIS, L. S., and PAPARIELLO, G. J. (1965) *Arch. Ophthal. (Chicago)*, **74**, 674
MCGUINNESS, R., and KNIGHT-JONES, D. (1968) *Brit. J. Ophthal.*, **52**, 777
VALVO, A. (1967) *Amer. J. Ophthal.*, **63**, 98
WISE, J. B. (1966) *Arch. Ophthal. (Chicago)*, **75**, 698

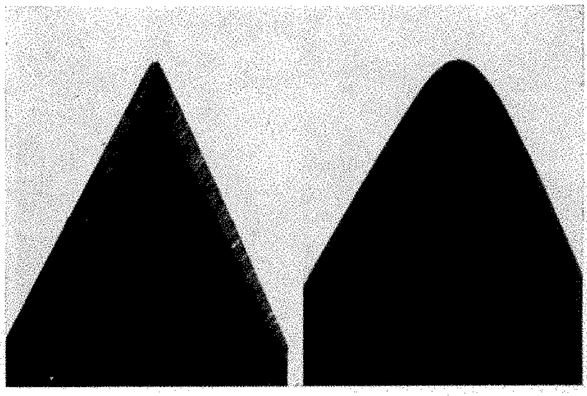
Brit. J. Ophthal. (1970) **54**, 500

A blunt-sharp Taylor knife

A. HAGEDOORN

Amsterdam

In "ab externo" incisions of the limbus, damage to the (protruding) iris should be prevented. The modification to the tip of the Taylor knife illustrated here contributes to the safety of the operation and may be of interest to those surgeons who are accustomed to using this instrument.



Received for publication December 22, 1969
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This modified knife was made by instrument-maker Charles G. van den Bosch

Brit. J. Ophthal. (1970) **54**, 501

Book reviews

Fractures of the Orbit (Fractures de l'orbite. Indications ophtalmologiques dans les techniques operatoires). By A. RENY and M. STRICKER. 1969. Pp. 174, 156 figs, bibl. Masson, Paris. (86*F*)

This excellent monograph in French by an ophthalmic surgeon and a maxillo-facial surgeon is based on their extensive collaborative experience in the treatment of facial injuries at Nancy, and represents a most valuable addition to the literature dealing with orbital injuries. As well as informative clinical photographs and radiographs there is a comprehensive bibliography of almost 400 references.

The work is divided into four parts. The first deals with the structural and functional aspects of binocular vision, radiological appearances, and electromyography. The second deals with the clinical and radiological manifestations of all types of fracture of the face and skull involving the orbit, the third with the pathogenesis of these injuries and their complications involving the eye, lids, lacrimal apparatus, and extra-ocular muscles, and the last with the treatment of these conditions in detail.

Throughout the work the chief emphasis is laid on the restoration of function and appearance to as near normal as possible, with particular reference to binocular single vision. The importance of the muscle duction test in the diagnosis of the incarceration of soft tissue is emphasized and the scope of electromyography is discussed.

This book can be highly recommended and should certainly be perused by those concerned in the management of orbital injuries, the incidence of which seems to be ever increasing.

Diagnosis and Management of Blow-out Fractures of the Orbit: Clinical, Radiological, and Surgical Aspects. By A. T. MILAUSKAS. 1969. Pp. 146, 50 figs. 3 pl., refs. Thomas, Springfield, Ill. ($8.50)

The author of this useful monograph on blow-out fractures of the orbit finds that these conditions are often inadequately treated and sometimes remain undiagnosed, usually because of unsatisfactory radiological examination. A concise account of the pathogenesis and clinical symptoms and signs of blow-out fractures serves as an introduction to the main part of the work, which deals in considerable detail with the radiological diagnosis of this type of injury. The text is illustrated with a large number of radiographs demonstrating the advantages and limitations of particular radiographic projections including those of Caldwell and Waters and the straight lateral view, and special views such as the 30° postero-anterior and the 20°/35° oblique projection for the examination of the floor and medial wall of the orbit.

A detailed description is given of the technique, limitations, and hazards of positive contrast orbitography, whereby a radio-opaque contrast medium is injected along the orbital floor outside the muscle cone in order to provide direct visual evidence of a fracture. This procedure is claimed to be particularly useful for the demonstration of minimal tissue prolapse into the antrum and for linear cracks with incarceration of soft tissue. The recently developed method of hypocycloid or polytomography, which in some centres is replacing the older techniques of linear tomography, is also described.

The final chapter consists of a short account by Morton Goldberg of the present policy in respect of the surgical management of blow-out fractures at the Wilmer Institute.

The quality of the radiographs is, in general, good, but it should be noted that a few have been printed the wrong way round in relation to the accompanying details (as has been noted in the text).

Essentials of Uveitis. By T. F. Schlaegel, Jr. 1969. Pp. 325 + viii, figs (some col.), refs. Little, Brown, Boston; Churchill, London. (£9 10*s*.)

Whereas much of the recent literature on uveitis has been concerned with experimental and immunological studies, this book is essentially a practical guide to diagnosis, investigation, and treatment, drawn mainly from the author's own experience of a large and well-documented series of cases. From a careful analysis of these he gives a clear guide to which investigations are of value and which are of little or no value.

The classification of uveitis is based on the clinical characteristics, particularly that part of the uveal tract which is involved. Non-specific treatment is discussed at length, with particular emphasis on the injection of steroids into Tenon's capsule and subconjunctivally. Immunosuppressive drugs were not found to be of value in cases of histoplasmosis.

The major part of the book consists of a description of the clinical types of uveitis associated with recognized aetiological factors, such as histoplasmosis, toxoplasmosis, virus infections, and toxocariasis, and systemic diseases, such as Reiter's syndrome and sarcoidosis. Miscellaneous types such as peripheral uveitis are also discussed, and there is a useful chapter on the differential diagnosis of uveitis and degenerative and neoplastic lesions.

Throughout the book there are references to recent papers, and this gives an excellent overall view of modern ideas on this subject. The presentation is clear and direct and all ophthalmologists who have to treat patients with uveitis will find the book helpful. It is well printed, adequately illustrated, and has a good index.

Notes

Post-Graduate Courses for Specialists in Ophthalmology

New York, September 9 to November 20, 1970

The Post-Graduate Institute of the New York Eye and Ear Infirmary announces the Thirteenth Series of Post-Graduate Courses for Specialists in Ophthalmology, to be given from September 9 to November 20, 1970, on the following subjects:

Advances in ocular prostheses; Biomicroscopy; Cataract surgery, Clinical perimetry, Corneal contact lenses; Corneal surgery; Diagnostic ultrasonography; Enucleation and evisceration; Fluorescein angiography; Glaucoma; Gonioscopy; Indirect ophthalmoscopy; Lacrimal sac surgery; Microsurgery; Motor anomalies; Neuro-ophthalmology; Ocular geriatrics; Ocular radiology; Ocular therapeutics; Ophthalmoscopy; Orbital anatomy; Pathology; Perimetry; Plastic eye surgery; Practical applanation tonometry; Radioisotopes in ophthalmology; Reading disability and the ophthalmologist; Refraction; Surgery of the orbit; Tonography and applanation tonometry; Uveitis.

At the conclusion of the regular series, a special 6-day course entitled "Review in Basic Sciences in Ophthalmology" will be given on December 7–12, 1970.

For catalogue and further information, please write to: Jane Stark, Registrar, Post-Graduate Institute, New York Eye and Ear Infirmary, 310 East 14th Street, New York, New York, 10003.

Second-Biennial Cataract Surgical Congress

Miami, Florida, February 6 to 10, 1971

The Second-Biennial Cataract Surgical Congress will be held at the Fontainebleau Hotel, Miami Beach, Florida, on February 6 to 10, 1971.

Approximately one hundred short papers or films on Cataract Surgery will be presented by approximately forty to fifty ophthalmologists. The subject of each paper will be discussed by a group of ten full-time faculty panellists.

To attend this meeting, early room reservations are recommended, as February is the height of the tourist season in South Florida. For further information please write to: Robert C. Welsh, M.D., 168 S.E. First Street, Miami, Florida 33131.

International Strabismological Association

I Congress, Mexico, March, 1970

The first Congress of the International Strabismological Association, which was formed in 1966, was held at the Pierre Marques Hotel, Acapulco, Mexico, on March 16 and 17, 1970.

The officers of the Association for 1966–70 were:

President:	T. Keith Lyle (*U.K.*)
Vice-Presidents:	Arthur Jampolsky (*U.S.A.*) Charles Thomas (*France*)
Secretary-Treasurer:	G. K. von Noorden (*U.S.A.*)
Editor:	Alfredo Arruga (*Spain*)
Associate Editor:	Joseph Lang (*Switzerland*)
Chairman of Programme Committee:	Hermann M. Burian (*U.S.A.*)

On the morning of March 10, after speeches of welcome from Dr. M. Puig Solanes (*Mexico*), President of the XXI International Congress, from Mr. T. Keith Lyle, President of the I.S.A., and from Dr. Emma Limón de Brown, chairman of the local organisation committee, a Symposium was held on "Early operations for strabismus", followed by a series of short papers on a variety of topics. The subsequent programme included symposia on "Non-surgical and surgical treatment of exodeviations" and "The use of prisms in the pre- and postoperative treatment".

The Bielchowsky lecture was given by Prof. G. K. von Noorden of the Johns Hopkins Hospital, Baltimore, on "Current concepts of amblyopia".

Amongst the many interesting papers given were "The use of membrane (Fresnel) prisms" by A. Jampolsky and "Intra-ocular muscle forces in strabismus" by A. B. Scott.

The following officers were elected for the years 1970–74:

President:	Hermann M. Burian (*U.S.A.*)
Vice-Presidents:	Renée Hugonnier (*France*) Alberto Ciancia (*Argentina*)
Secretary-Treasurer:	Gunter K. von Noorden (*U.S.A.*)
Editor:	Peter Fells (*U.K.*)
Consulting Editors:	Alfredo Arruga (*Spain*) Joseph Lang (*Switzerland*)

The next meeting of the Association will be held in France immediately before or after the next International Congress of Ophthalmology (which is to be held in Paris in 1974), but the date is not yet fixed.

Any qualified medical practitioner interested in the problems of strabismus and ocular motility who wishes to join the Association should write to the Secretary-Treasurer: Prof. G. K. von Noorden, M.D., The Wilmer Institute, Johns Hopkins Hospital, Baltimore, Maryland, U.S.A.

International Council of Ophthalmology

International Federation of Ophthalmological Societies

Meetings in Mexico, March, 1970

The International Council of Ophthalmology and the International Federation of Ophthalmological Societies met in Mexico on the occasion of the XXI International Congress of Ophthalmology in March, 1970. After the presentation of a report by Prof. Streiff, Prof. Nordmann, Dr. Cuendet, and Dr. Schellhorn on the coding of ocular diseases, a perforated card for the international coding system of eye disorders was accepted.

Concerning contact lenses, the following motion was approved:

"The indication, prescription, clinical and optical fitting, and control of contact lenses must remain medical work, for which only the ophthalmologist must assume responsibility. Non-medical technicians, even those who have specialized in optics, may participate in the optical fitting only as paramedical assistants in the doctor's office. These assistants must be subject to the restrictions imposed by the regulations concerning medical auxiliaries."

Criteria for the standardization of tonometers were also accepted.

A committee for the review and study of visual standards for driving as adopted by the American Medical Association Committee on medical aspects of automotive safety was nominated.

The XXII International Congress of Ophthalmology is to be held in 1974 in Paris.

The Ophthalmological Societies of Iraq, Bolivia, Thailand, Morocco and Lebanon, and the Asia-Pacific Academy of Ophthalmology were elected members of the International Federation.

Prof. Brégeat, Dr. Moutinho, Prof. Hilton Rocha, Prof. Sautter, Prof. Mrs. Vannas, Mr. Stephen Miller, and Dr. M. Hogan were elected members of the International Council of Ophthalmology.

Prof. Jules François (*Ghent*) was elected President of the International Council of Ophthalmology and of the International Federation of Ophthalmological Societies, Dr. M. Hogan (*San Francisco*) Vice-president, Prof. Streiff (*Lausanne*) Treasurer, and Prof. A. Dubois-Poulsen (*Paris*) Secretary.

European Ophthalmological Society

IV Congress, Budapest, April 17–21, 1972

The fourth congress of the European Ophthalmological Society will be held in Budapest in April, 1972, under the presidency of Prof. Mrs. M. Radnót. The topic to be discussed is functional examinations in ophthalmology.

For all information, please write to Prof. Mrs. M. Radnót, First Department of Ophthalmology, University Medical School, Illés u. 15, Budapest VIII, Hungary.

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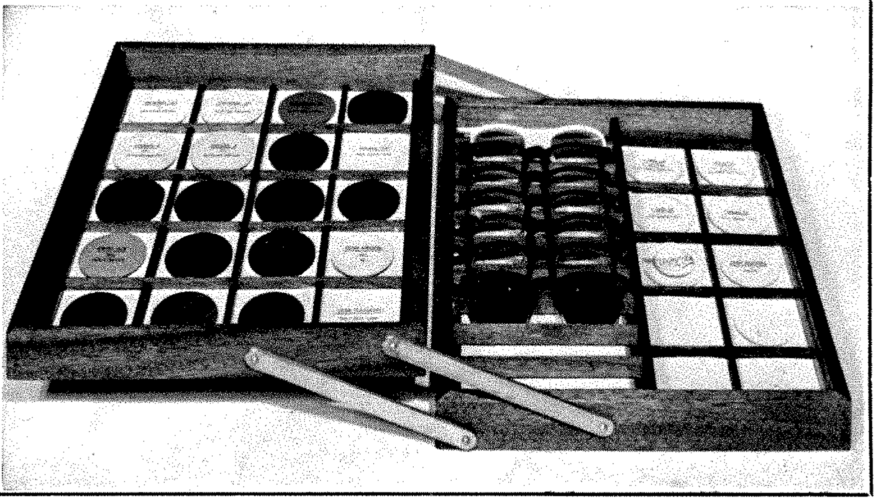

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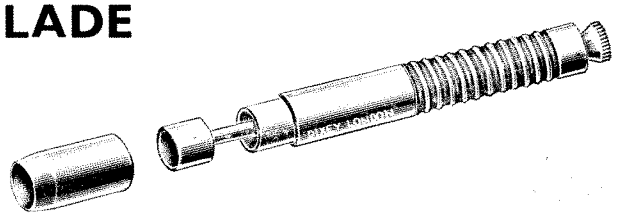

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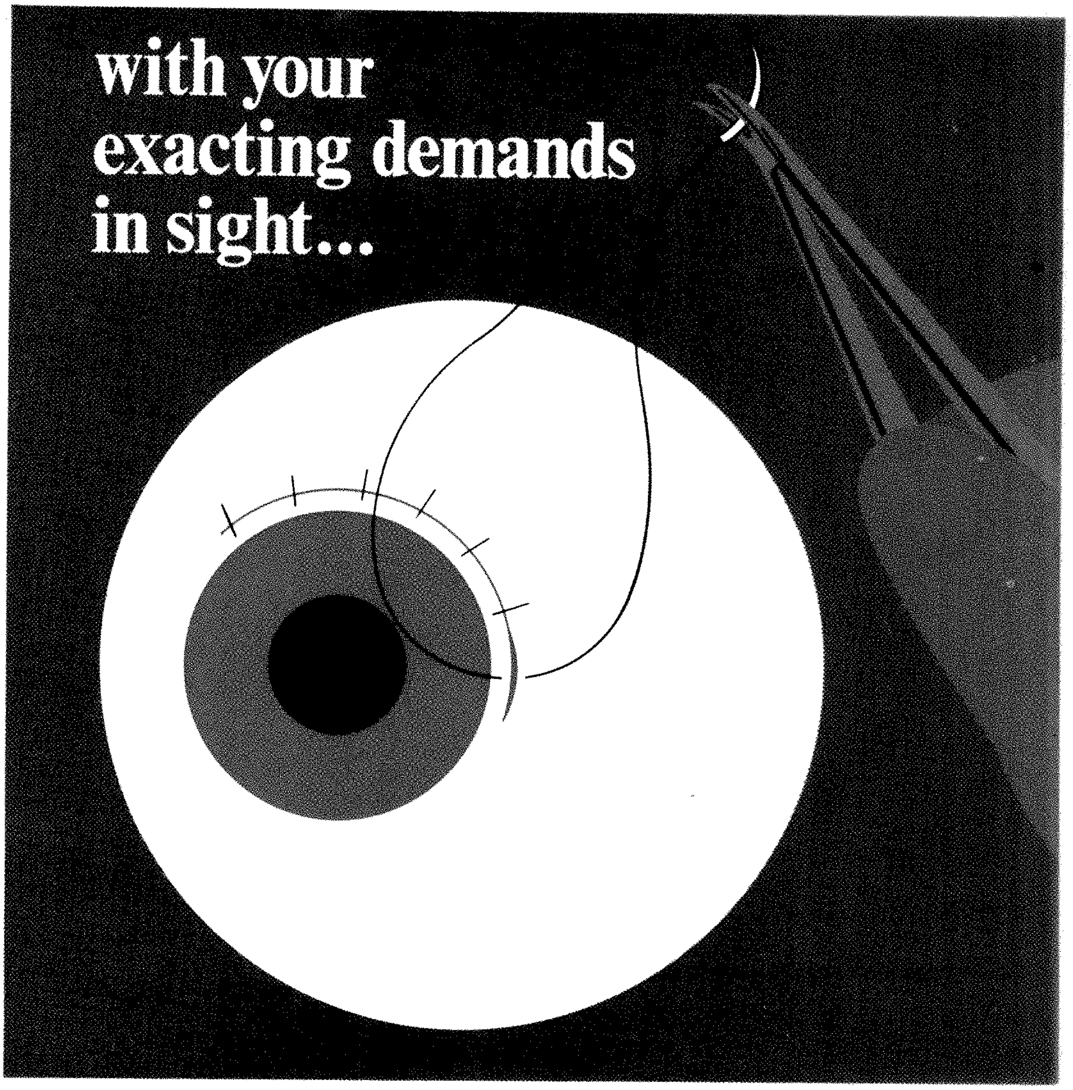

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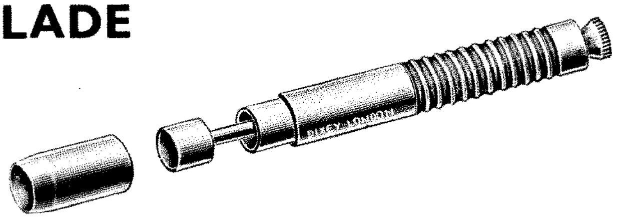

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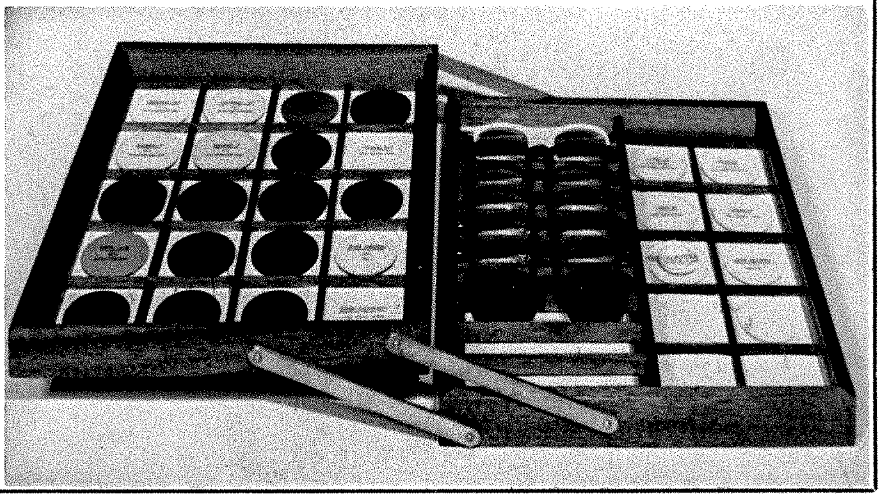

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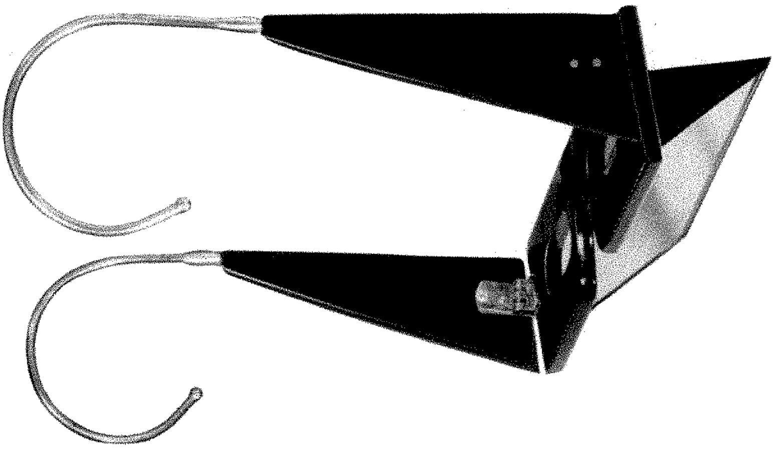

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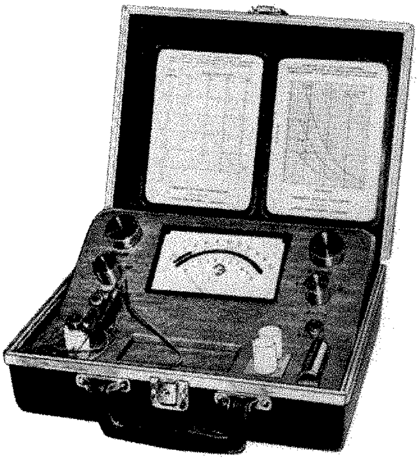

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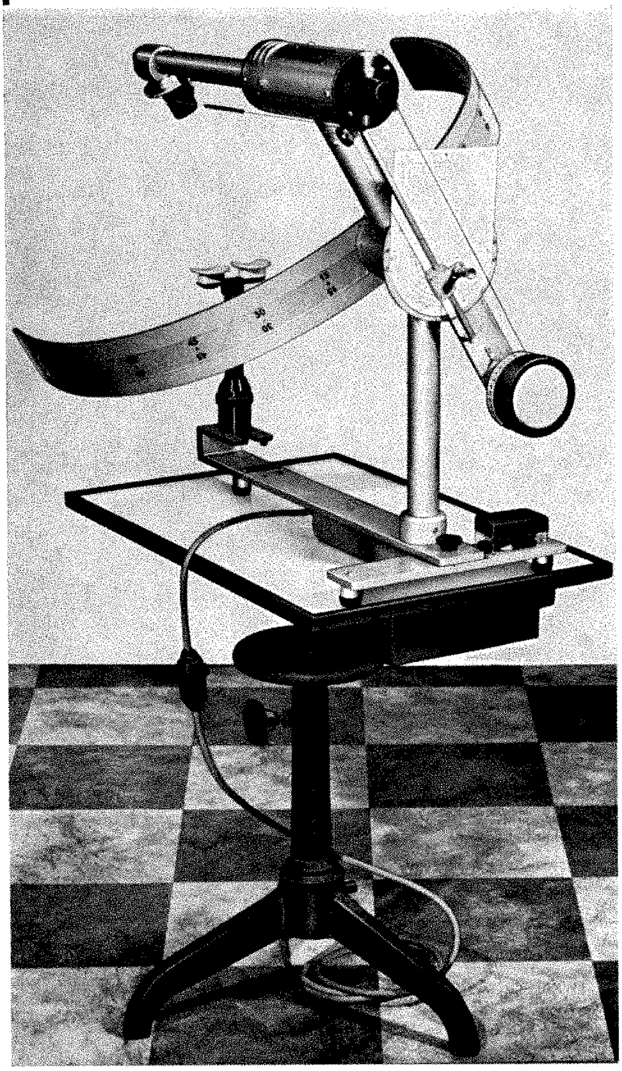

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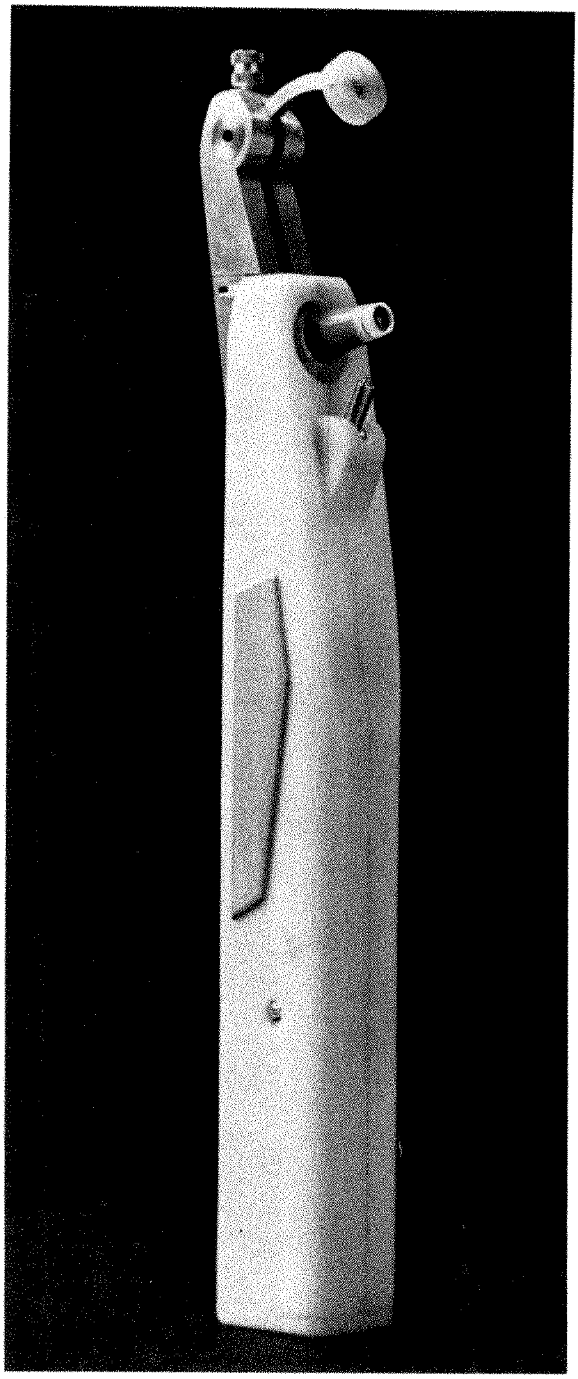

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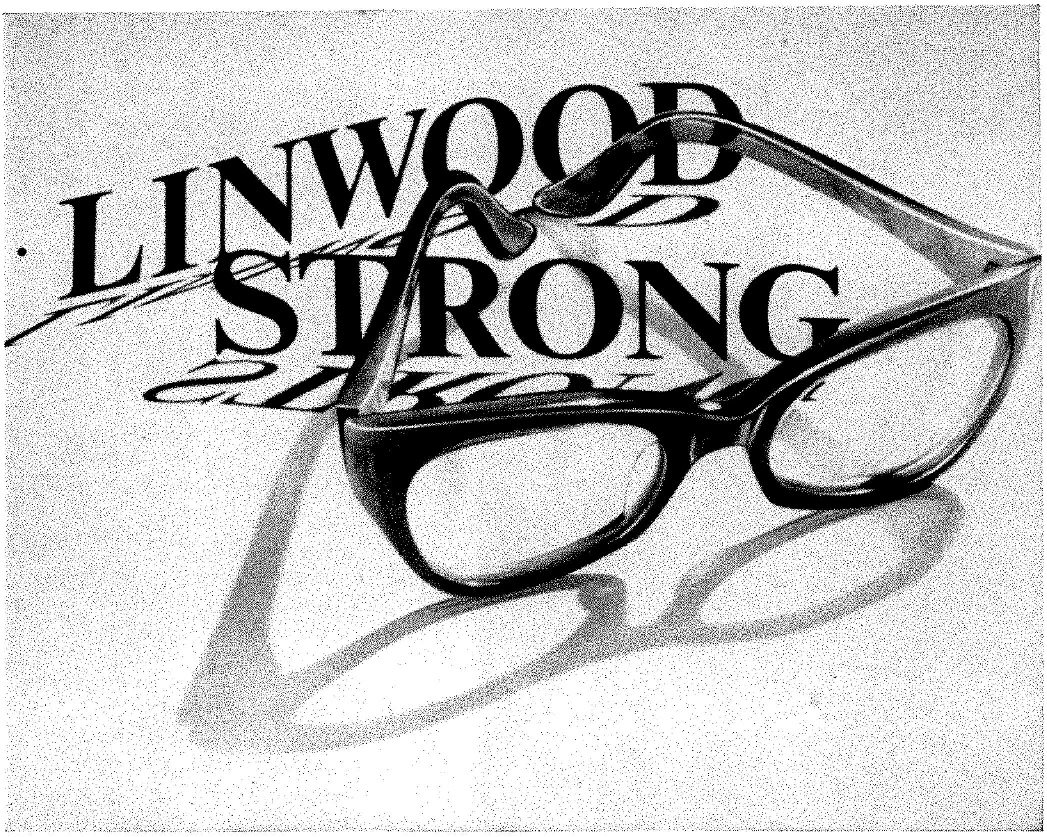

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Communications

Radiation retinopathy after the application of a cobalt plaque

Report of three cases

M. A. BEDFORD, C. BEDOTTO*, AND P. A. MACFAUL
Moorfields Eye Hospital and St. Bartholomew's Hospital, London

Radiation damage to the retinal vascular system has been held responsible for small vessel occlusion, neovascularization, haemorrhages, and exudates when the whole eye has been involved during the course of therapeutic irradiation for the treatment of retinoblastoma (Martin and Reese, 1945; Howard, 1966), basal cell carcinoma of eyelids or nose, and carcinoma of the paranasal sinuses (Perrers-Taylor, Brinkley, and Reynolds, 1965; Chee, 1968; Gass, 1968).

Local radiation treatment for intraocular neoplasms was introduced by Foster Moore (1935) using radon seeds. From 1948 onwards, the physical principles established by Innes (1964), working in conjunction with Stallard, led to the development of the cobalt 60-applicators, which are now used in many centres throughout the world, not only for the treatment of retinoblastoma but also in certain cases of malignant melanoma of the choroid (Stallard, 1968).

Retinal vascular complications after this form of therapy have been noted in the literature (Stallard, 1961, 1966) but have received little emphasis. However, in a recent study from this unit of ocular complications associated with various types of therapeutic irradiation (MacFaul and Bedford, 1970), attention was drawn to certain vascular lesions which, in some cases, may result in loss of vision in the treated eye.

The purpose of this paper is to report three cases of choroidal malignant melanoma treated with a cobalt 60-applicator and investigated by fluorescein angiography, in which delayed visual loss was associated with retinal vascular occlusions of varying degree.

Case reports

Case 1, a 50-year-old man, was first seen in June, 1967, with an elevated pigmented lesion and associated serous retinal detachment in the infero-nasal quadrant of the left eye about 1·5 mm. from the optic disc; the corrected visual acuity was 6/5. The right eye was normal. Fluorescence fundus angiography showed a pattern compatible with the clinical diagnosis of malignant melanoma of the choroid.

On August 23, 1967, a 7·5 mm. circular cobalt plaque was applied over the base of the tumour and left in place for 14 days, giving an estimated dose of 8,000 r to the summit of the tumour. Over the next 2 months the serous detachment cleared completely and 6 months after treatment the

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tumour was noted to be flat and apparently inert. In May, 1968, 9 months after treatment, haemorrhages were observed close to the optic disc. In July, 1968, the fundus showed retinal haemorrhages, cotton-wool spots, and oedema supero-temporal to the optic disc (Fig. 1); angiography showed evidence of occlusion of the small vessels in the upper temporal quadrant, but the main arterial and venous channels were still patent (Figs 2 and 3). In October, 1968, there were haemorrhages and exudates along the inferior temporal vessels, the visual acuity having dropped to 6/18.

(1)

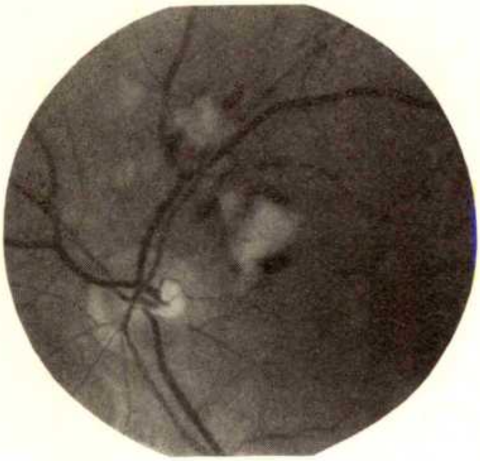
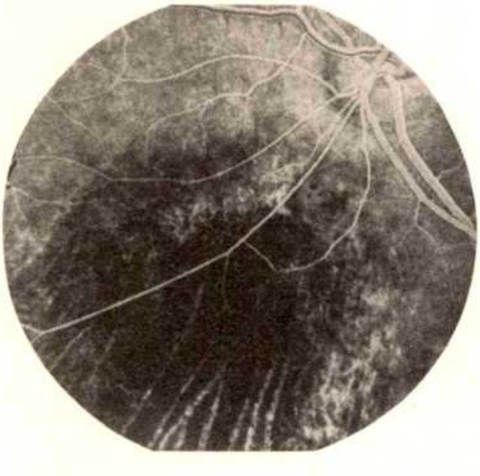


FIG. 1 *Case 2. Fundus photograph, 11 months after treatment, showing haemorrhages and cotton-wool spots along superior temporal vessels, the site of the tumour being infero-nasal*

(2)



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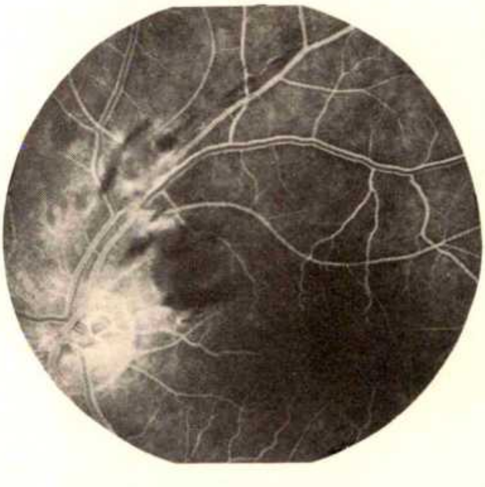

FIG. 2 *Case 1. Angiogram, showing choroidal atrophy in treated area and patency of major retinal vessels*

FIG. 3 *Case 1. Angiogram, showing patency of large supero-temporal vessels with evidence of occlusion of the small vessels and early fluorescein leakage into the infarcted area of the retina*

In May, 1969, 21 months after irradiation, the visual acuity was still 6/18 and, although the supero-temporal vascular changes had regressed, considerable changes were still present in the lower temporal quadrant; angiography at this time demonstrated the patency of the major infero-temporal vessels but also showed extensive areas of capillary closure and telangiectasia (Figs 4 and 5, opposite).

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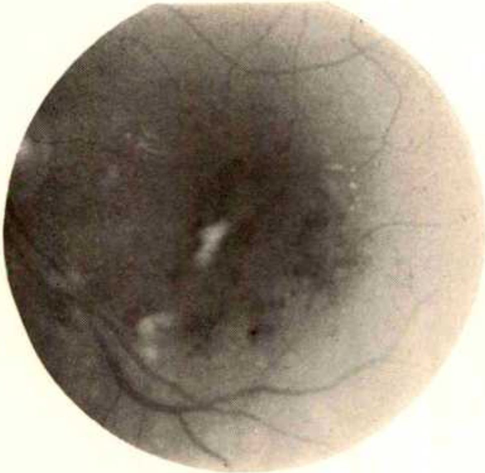

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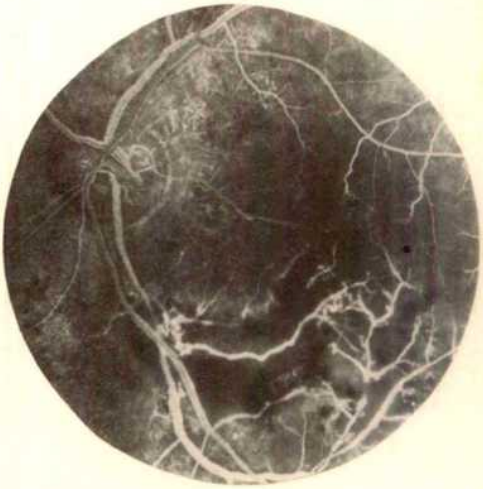


FIG. 4 *Case* 1. *Fundus photograph,* 21 *months after irradiation, showing oedema with haemorrhages and exudates along the inferior temporal vessels, extending towards the macula*

FIG. 5 *Case* 1. *Angiogram, showing patency of major retinal vessels, capillary occlusion, telangiectasia, and new vessel formation in lower temporal quadrant*

Case 2, a 51-year-old woman, was first seen in May, 1964, complaining of blurred vision in the right eye for 3 weeks; the visual acuity was 6/9 and there was a lower temporal visual field defect. A diffuse, slightly elevated pigmented lesion was seen almost surrounding the optic disc. The left eye was normal. Although a malignant melanoma of the choroid seemed the most likely diagnosis, it was decided to observe the lesion as a metastasis could not be ruled out. Over the next 9 months visual acuity fell to 6/24; the appearance of a secondary serous retinal detachment and slow extension of the lesion towards the macula favoured the diagnosis of malignant melanoma.

In August, 1965, a C-shaped cobalt plaque was applied to the posterior pole of the eye and left in position for 16 days, giving an estimated dose of 8,000 r to the summit of the tumour; 3 months later the visual acuity was 6/6 and the serous detachment had disappeared. In June, 1966, the area of the tumour was flat and showed radiation scarring. In June, 1967, visual acuity had dropped to 6/60: although the tumour was still inert, haemorrhages and exudates were present below the optic disc and white sheathing of the upper nasal retinal vessels was subsequently noted. In November, 1968, visual acuity remained at 6/60 and the eye was divergent; the retinal vessels showed marked radiation changes with extension of the sheathing out to the periphery (Fig. 6).

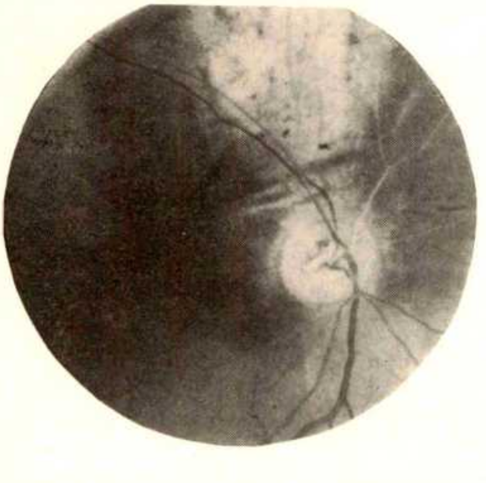
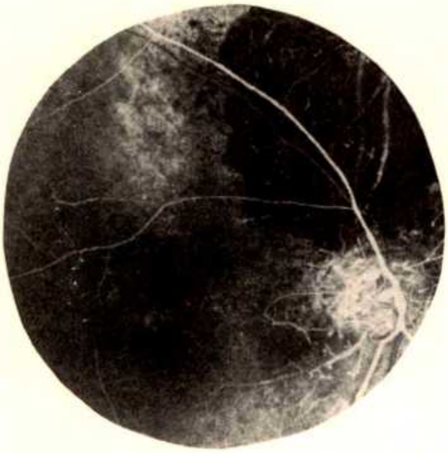


FIG. 6 *Case* 2. *Fundus photograph,* 3 *years after irradiation, showing extensive choroidal atrophy in treated area and occlusion of superior nasal vessels*

Fluorescein angiography in May, 1969, showed loss of capillaries in the treated area with microaneurysms and new vessel formation on and around the optic disc (Fig. 7) and occlusion of the supero-nasal retinal vessels but patency of the supero-temporal vessels (Fig. 8).

(7)



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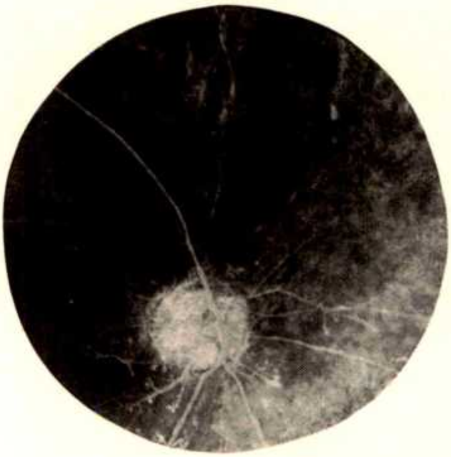


FIG. 7 *Case 2. Angiogram, showing extensive capillary occlusion, microaneurysms at the edge of the treated area, and new vessel formation on and around the optic disc*

FIG. 8 *Case 2. Angiogram, showing occlusion of superior nasal artery and to a lesser degree of the vein; there is extensive choroidal vascular occlusion in the treated area*

Case 3, a 53-year-old man, was first seen in February, 1967, with a 3-month history of loss of the temporal visual field in the right eye. On examination the visual acuity was 6/5 and the temporal field defect was confirmed. In the supero-nasal quadrant of the right fundus a large lightly-pigmented tumour was seen and clinical diagnosis of malignant melanoma of the choroid was made. The left eye was completely normal.

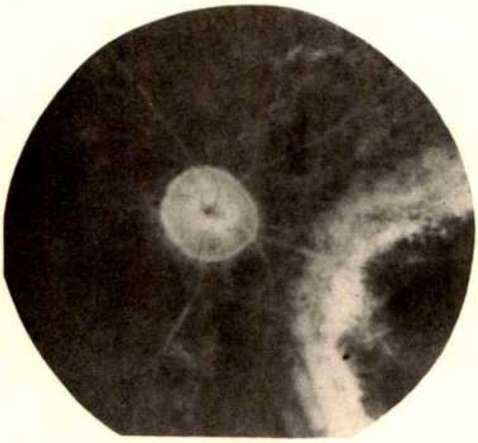
In February, 1967, a 15 mm. circular cobalt plaque was applied over the base of the tumour and left in place for 14 days, giving an estimated dose of 8,000 r to the summit of the tumour. During the next 6 months the tumour regressed and in September, 1967, the visual acuity was still 6/6 but a haemorrhage was observed close to the optic disc on the nasal side. In March, 1968, a year after treatment, the visual acuity had deteriorated to 6/18, and this was associated with the onset of marked retinal vessel changes, although the area of the tumour remained flat and inert. In May, 1968, the patient found on waking one morning that he had lost the vision of the right eye and, when seen, the fundus appearance was that of an occlusion of the central retinal artery. Since then there has been no perception of light in the right eye, with signs of optic atrophy, sheathing of the vessels near the disc, and telangiectatic changes in the peripheral retina.

The appearance of the posterior pole in February, 1969, is shown in Fig. 9 (opposite); fluorescein angiography showed the picture of an occlusion of the central retinal artery and no evidence of active tumour (Fig. 10, opposite).

Discussion

These three cases show that localized radiation damage to the retinal blood vessels near the optic disc can lead to severe visual loss; less severe damage has previously been reported after irradiation of the whole eye, the chief defects comprising retinal capillary damage with haemorrhages, exudates, and retinal oedema.

(9)



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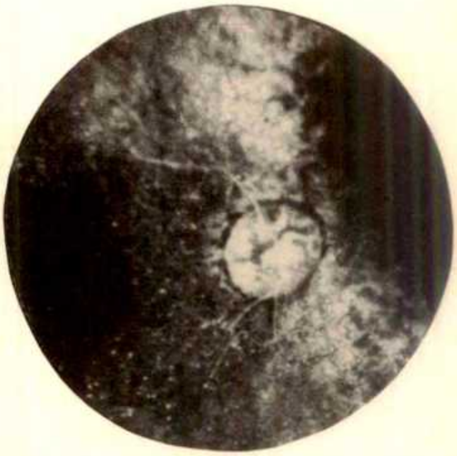

FIG. 9 *Case* 3. *Appearance of the fundus*, 2 *years after application of a cobalt plaque, showing occlusion of central retinal artery and marked pallor of optic disc*

FIG. 10 *Case* 3. *Angiogram, showing almost complete occlusion of central retinal artery*

Our cases were treated with cobalt 60-applicators, which deliver a massive dose of gamma rays to a small area: a tumourcidal dose of approximately 8,000 r to the summit of the tumour necessitates about 40,000 r to the sclera and choroid over the base of the tumour in 2 weeks. It is now apparent that these high levels of radiation will damage not only capillaries but also the larger retinal vessels; when a large vessel in or near the optic disc becomes occluded the visual loss can be profound. For this reason, therefore, we feel that a cobalt plaque should not be placed within 5 mm. of the optic disc unless the patient is prepared to accept the possibility of permanent severe loss of vision.

Summary

Three cases of retinal vascular occlusion of varying degree following the treatment of malignant melanoma of the choroid with cobalt 60-applicators are described; the limitations of this form of treatment for melanomata close to the optic disc are discussed.

We should like to thank the Medical Illustration Department at the Institute of Ophthalmology, London, for help with the illustrations and Miss Heather Payne for secretarial assistance.

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Double-blind cross-over comparison of aceclidine and pilocarpine in open-angle glaucoma

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Aceclidine hydrochloride (3-acetoxyquinuclidine, "Glaucostat": Chibret) used topically in a strength of 2 per cent. is a parasympathomimetic drug acting directly on the motor end-plate (cholinergic nerve-endings). It is suitable for administration as eye drops, penetrating rapidly into the anterior chamber. It is a synthetic substance and was first prepared in Russia by Rubitzov and Miklina (1960). The name "Aceclidine" was coined by Mashkovski and Zaitzeva (1960), who studied its pharmacological aspects. It was also described by Sharts and Shulpina (1961).

Numerous clinical trials in Russia, France, and Italy and in other countries have led to its widespread use on the continent of Europe, including the U.S.S.R. In several centres it is used routinely as an alternative to pilocarpine or when pilocarpine fails.

The drug has also been investigated in the United States of America by Lieberman and Leopold (1967), who described a definite lowering of intraocular pressure with no corresponding increase in facility of outflow. Aceclidine is not in clinical use in the U.S.A.

Our interest was stimulated by these early reports. No fully satisfactory topical direct-acting parasympathomimetic drug is available as an alternative to pilocarpine if for any reason this is or becomes unsuitable. In such cases resort is usually made to cholinesterase-inhibiting substances—eserine, prostigmine (neostigmine), or one of the "irreversible" cholinesterase inhibitors, di-isopropylfluorophosphonate (DFP), phospholine iodide, demecarium bromide, etc.

The use of the latter group of drugs is not without its disadvantages or dangers. Of the available direct parasympathetic stimulating drops, acetylcholine itself is too unstable to remain in solution for more than a few minutes. Carcholin (carbachol, Doryl, carbamylcholine chloride, a synthetic drug) 0·75 to 3 per cent. has poor corneal penetration, being hydrophilic, and must be used with a wetting agent in methyl cellulose (Shaffer, 1967), or as a dry suspension in anhydrous vehicles (Swan, 1959). Methacholine (Mecholyl) 10 to 20 per cent. is unstable and short-acting and must be used every 5 to 10 minutes. Arecoline, the alkaloid of the betel nut, was tried in ophthalmology in 1895 but never used in practice. Its formula is similar to that of aceclidine. Furmethide (furfuryl methyl ammonium iodide) and urecholine (urethane of beta-methyl choline) have also been abandoned.

Among the obvious advantages that aceclidine appears to offer over the preceding drugs are its stability, penetration, and long shelf-life.

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Pharmacology

Aceclidine is 3-acetoxyquinuclidine (cf. molecular structure. Figure).

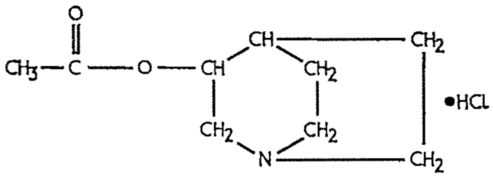

FIGURE *Structural formula of aceclidine hydrochloride*

It is available as:

(*i*) The salicylate (molecular weight 308·34, a 2 per cent. concentration corresponding to an 0·065 molar solution). This is the preparation used by Lieberman and Leopold (1967). A 2 per cent. solution of aceclidine salicylate is only 0·79 times as concentrated a molar solution as 2 per cent. pilocarpine nitrate.

(*ii*) Aceclidine hydrochloride (Glaucostat) with a molecular weight of 205·5. A 2 per cent. solution of the hydrochloride corresponds to an 0·097 molar solution. It is interesting that pilocarpine HCl has a molecular weight of 244·71, a 2 per cent. solution corresponding to an 0·82 molar solution, *i.e.* intermediate between the two forms of aceclidine (Table I).

Table I *Formula of 2 per cent. aceclidine hydrochloride eye drops*

3-acetoxyquinuclidine hydrochloride	2·0 g.
Boric acid	1·8 g.
Sodium borate	0·13 g.
Distilled water	100 ml.

Aceclidine has a potent parasympathomimetic action in man and experimental animals and a very weak anticholinesterase activity. This action is accordingly abolished or greatly weakened by atropine but almost unaffected by cholinesterase (Mashkovski and Zaitzeva, 1960). In experimental animals it possesses a parasympathomimetic action superior to that of a similar dose of pilocarpine. It is less toxic than pilocarpine, the L.D.50 being 0·116 g./kg. (in mouse intraperitoneally) and 0·105 g./kg. (in rat)—approximately twice that of pilocarpine. No tachyphylaxis has been noted after repeated doses in contrast to that seen with pilocarpine (Yankelowitz, 1965).

It is prepared in a lyophilized form and is mixed at the time of dispensing. In powder form it undergoes only a 5 per cent. loss of activity after 3 months at 37°C. and can be used for up to 3 years. In solution a similar loss of activity occurs after 30 days at 22°C. (Tarrerias and Vassallo, 1967). The pH of the hydrochloride before bottling is 6·60. That of a 2 per cent. pilocarpine HCl solution is 4·8. On storing, aceclidine undergoes a slight fall in pH to 6·43, whereas pilocarpine tends to become more acidic.

No irritation in human subjects is recorded with a 2 to 4 per cent. solution, or in the rabbit eye with a 20 per cent. solution (Yankelowitz, 1965). The drug penetrates rapidly into the anterior chamber (Rouher, 1966).

Description of the trial

The object of the trial was a direct comparison of the effect on the same eyes and under identical conditions of gutt. pilocarpine 2 per cent. and gutt. aceclidine HCl 2 per cent., both used three times a day. One eye received pilocarpine and the other aceclidine. The eyes were examined at the end of one week of therapy, and after a fixed interval, 1½ hours, from the last instillation. The following conditions were thought to be desirable:

(*a*) Double-blind conditions to ensure lack of bias on the part of the patient in describing the symptoms, and greater objectivity on the part of the observer.

(*b*) Use of a placebo for one week to each eye to eliminate the effect of previous medication; it is claimed that 32 hours are sufficient for this purpose (Agugini and Stecchi, 1968).

(*c*) Cross-over after a further week of placebo.

MATERIAL AND METHODS

The trial covered a total of 54 eyes (27 cases). All were established cases of open-angle (chronic simple) glaucoma undergoing medical treatment (with pilocarpine: 36 eyes; pilocarpine and eserine: 3 eyes; pilocarpine and neutral adrenaline: 16 eyes; phospholine iodide and neutral adrenaline: 1 eye; adrenaline alone: 2 eyes).

SUITABILITY OF CASES

(1) No patient undergoing therapy with a carbonic anhydrase inhibitor and only one eye previously on a powerful anticholinesterase drug was included in the test. (In two eyes neutral adrenaline was continued during the trial.)

(2) Visual acuity had to be at least 1/60 in each eye to allow tonography to be performed in both eyes.

(3) Patients fulfilling the above requirements were considered suitable for the "full trial" (see later) only if their anterior chamber depth and configuration were such that angle closure was considered unlikely to occur when miotic therapy was interrupted for a week. Patients with a previously-recorded high level of intraocular pressure (greater than 28–30 mm. Hg) were also considered unsuitable for the full trial.

In Groups 2 and 3, the non-placebo or shorter trial was carried out.

A. Full Trial (34 eyes) (Table IIA, opposite)

(1) *First visit*: Nature of trial explained: whatever the frequency of previous medication, drops to be used three times a day during trial (7.0 a.m., 2.0 p.m., and 10.0 p.m. whenever possible).

On day of attendance at clinic, however, mid-day instillation set at a specified hour (usually 1.30 or 2.0 p.m.) so that a constant interval should elapse before tonometry. Patient requested to observe and note various symptoms (see later) following use of drops, with special attention to comparison of the two eyes.

Two bottles dispensed marked Right and Left containing placebo (physiological saline) to enable patients to practise adhering to new routine of treatment.

(2) *Second visit* (after 7 days).

(*a*) Questionnaire: contrasting and comparing effects on the two eyes as regards: pain/

Table IIA *Clinical particulars of 17 full trial cases (34 eyes)*

Case no.	*Eye*	*Po*	*P pilo*	*P acec*	*Co*	*C pilo*	*C acec*	*Po/Co*	*Po/C pilo*	*Po/C acec*
1	R	29	20	26	0·15	0·24	0·18	193	83	144
	L	32	27	26	0·11	0·20	0·18	290	130	144
2	R	23	14	23	0·13	0·27	0·12	176	51	191
	L	24	20	17	0·20	0·15	0·17	120	133	100
3	R	24	14	18	0·19	0·33	0·20	105	42	90
	L	24·5	16	17	0·20	0·22	0·24	100	72	70
4	R	22	16	20·66	0·13	0·23	0·20	176	52	150
	L	22	21·33	18	0·12	0·26	0·15	250	80	140
5	R	30	22	21·66	0·07	0·25	0·16	430	88	137
	L	36	20·33	26	0·07	0·19	0·21	514	105	123
6	R	26	13·0	18	0·13	0·25	0·27	200	52	96
	L	29·66	18·50	18	0·20	0·25	0·27	150	112	66
7	R	20·33	18	10	0·30	0·41	0·41	66	43	37
	L	17·33	9	16	0·40	0·45	0·45	42	22	34
8	R	26·5	17·33	19·66	0·06	0·20	0·18	450	85	111
	L	29·5	16·33	16·66	0·06	0·16	0·26	500	100	64
9	R	18	24·66	33·66	0·05	0·11	0·10	360	218	300
	L	20	22	20·33	0·15	0·12	0·20	133	183	100
10	R	26	21·66	19·66	0·16	0·13	0·13	162	154	154
	L	22	18·66	18·33	0·15	0·20	0·20	147	95	95
11	R	22·66	16·8	17·66	0·14	0·27	0·30	165	63	70
	L	23·33	20·0	19·66	0·14	0·19	0·24	165	115	84
12	R	35·33	20·33	21·66	0·07	0·13	0·20	515	154	110
	L	30·66	20·33	20·5	0·10	0·15	0·13	300	134	154
13	R	22·0	21·0	17·33	0·25	0·20	0·19	88	105	95
	L	23·66	21·66	23·33	0·21	0·16	0·16	114	136	144
14	R	25·33	24·66	26·0	0·13	0·13	0·13	195	195	200
	L	23·0	19·33	19·0	0·21	0·15	0·19	110	134	100
15	R	19·0	16·0	18·0	0·23	0·26	0·25	83	61	64
	L	20·33	19·0	18·0	0·24	0·23	0·23	84	83	75
16	R	23·0	20·0	22·0	0·25	0·24	0·25	88	83	88
	L	23·0	22·0	19·33	0·30	0·25	0·29	73	88	65
17	R	33·0	19·0	30·66	0·11	0·17	0·06	290	112	500
	L	30·0	17·66	17·0	0·10	0·17	0·17	300	106	100

Po = pressure after placebo
P pilo = pressure after pilocarpine
P acec = pressure after aceclidine
Co = outflow after placebo
C pilo = outflow after pilocarpine
C acec = outflow after aceclidine
Po/Co = Po/C after placebo
Po/C pilo = Po/C after pilocarpine
Po/C acec = Po/C after aceclidine

browache, smarting, red eye, watering eye, running nostrils, watering mouth, blurring and/or darkening of vision, sneezing, gastrointestinal symptoms (cramps, diarrhoea).

(*b*) Observation of relative hyperaemia of two eyes.

(*c*) Estimation of pupil size either by using the graticule on Goldmann's perimeter, or by direct confrontation with the pupillometry wheel on the Hamblin/Morton ophthalmoscope under uniform conditions of lighting and fixing distant object. With practice, accuracy of 0·25 mm. is possible (*e.g.* between the 2·5 and 3·0 mm. marks), considered adequate for the purposes of the test.

(*d*) Applanation tonometry: using Goldmann tonometer mounted on Haag-Streit 900 slit lamp, checked for accuracy before each session with calibration device for 20 and 60 mm. Hg. Three readings made on each eye, changing eyes between each reading, and mean pressure recorded.

(*e*) Tonography: using Schwarzer recording tonometer. P_0 taken as applanation reading. As far as possible 45 to 60 minutes allowed to elapse between recording of two eyes. Only good tracings accepted. Correction for scleral rigidity not included.

(*f*) Pilocarpine 2 per cent. and aceclidine 2 per cent. dispensed at Hospital Pharmacy in bottles marked Right and Left plus a code symbol corresponding to a number in a scientifically randomized series.

(3) *Third visit* (end of second week). Questionnaire, etc., as on second visit.

Two sets of drops issued; (*a*) Two bottles of placebo for third week; (*b*) Two bottles of pilocarpine/aceclidine in sealed envelope for use at beginning of week four (date specified on envelope).

(4) *Fourth visit* (14 days after third visit). Procedure as at third visit.

At the conclusion of the trial each patient resumed his previous therapy.

B. Non-placebo or "Short" Trial (20 eyes) (Table IIB)

Table IIB *Clinical particulars of* 10 *non-placebo cases* (20 *eyes*)

Case no.	*Eye*	*P acec*	*P pilo*	*C acec*	*C pilo*	P_0/C *acec*	P_0/C *pilo*
1	R	23	22·66	0·13	0·13	175	175
	L	24·1	25·0	0·09	0·10	265	250
2	R	20·33	19·88	0·13	0·30	154	67
	L	16·0	15·66	0·26	0·12	62	133
3	R	24·0	24·33	0·26	0·16	92	150
	L	24·0	23·16	0·13	0·21	185	110
4	R	21·66	14·0	0·12	0·11	183	128
	L	18·0	13·0	0·08	0·11	222	118
5	R	30·66	28·0	0·10	0·14	310	200
	L	28·0	27·33	0·10	0·18	280	150
6	R	37·0	30·0	0·18	0·15	205	200
	L	32·0	26·66	0·11	0·14	280	194
7	R	18·66	19·33	0·17	0·24	112	83
	L	21·33	17·66	0·19	0·17	113	106
8	R	23·33	21·66	0·31	0·20	77	110
	L	20·0	20·0	0·19	0·24	105	83
9	R	27·33	37·33	0·10	0·05	280	740
	L	24·0	16·66	0·09	0·12	255	142
10	R	28·33	22·66	0·16	0·21	179	110
	L	22·0	22·33	0 09	0·14	244	161

One eye placed on gutt. pilocarpine 2 per cent. and the other on gutt. aceclidine 2 per cent. (according to the randomized series) for a period of 2 weeks. After 2 weeks, cross-over carried out.

Trial lasted 4 weeks as for standard trial, but included only three visits, 14 days apart, at which the procedure was the same as for the standard trial.

Results

The results were evaluated statistically, using Student's *t*-test. The *t* and P values are given in Table III.

Table III *Statistical evaluation of results*

(1) *Comparison of pilocarpine and aceclidine with placebo (full trial cases only)*

Drug	*Mean intraocular pressure*	*C-value*	*P₀/C*	*Pupil diameter*
Pilocarpine	Per cent fall 25·54 t = 6·8 P < 0·001	Per cent. rise 34·37 t = 4·3 P < 0·001	Per cent. fall 54·13 t = 4·8 P < 0·001	Per cent. reduction 47·8 t = 14·2 P ≪ 0·001
Aceclidine	Per cent. fall 19·10 t = 5·0 P < 0·001	Per cent. rise 31·25 t = 4·6 P < 0·001	Per cent. fall 41·16 t = 3·6 P < 0·001	Per cent. reduction 52·43 t = 12·7 P ≪ 0·001

(2) *Comparison of pilocarpine with aceclidine*

Drug		*Pilocarpine*	*Aceclidine*	*Difference*	*t*	*P*
Mean I.O.P. (mm. Hg)	All cases	20·28	21·81	1·53	3·49	> 0·05
	Full trial	19·05	20·40	1·35	2·33	> 0·05
Mean C-value	All cases	0·20	0·19	0·01	1·09	> 0·15
	Full trial	0·215	0·21	0·005	0·78	> 0·15
Mean P_0/C	All cases	110·54	147·65	37·11	1·67	> 0·15
	Full trial	102·0	123·38	21·38	1·79	> 0·15
Pupil diameter (mm.)	Full trial	1·94	1·82	0·12	1·24	> 0·15

(1) INTRAOCULAR PRESSURE

The mean intraocular pressure in cases on placebo was 25·18 mm. Hg. That in all cases on pilocarpine was 20·28 mm. Hg (S.E. 0·58). That for the 34 eyes on the full trial was 19·05 mm. Hg, and for the 20 eyes on the non-placebo trial 22·37 mm. Hg. The mean pressure for all cases on aceclidine was 21·81 mm. Hg (S.E. 0·71), for all cases on the full trial 20·40 mm. Hg, and for those on the non-placebo trial 24·19 mm. Hg. The percentage fall in pressure from placebo to pilocarpine was 24·5 per cent. and from placebo to aceclidine 19·10 per cent. Both drugs produced a statistically significant fall as compared to the placebo. The difference between the two was not significant.

(2) AQUEOUS OUTFLOW

(*a*) *Outflow coefficient*

Mean coefficient value (C-value) on placebo 0·16 (S.E. 0·013).

Cases on pilocarpine 0·20 (S.E. 0·013) (full cases 0·215; non-placebo cases 0·16).

Cases on aceclidine 0·19 (S.E. 0·013) (full cases 0·21; non-placebo cases 0·15).

Percentage rise from placebo to pilocarpine 34·37 per cent., that from placebo to aceclidine 31·25 per cent. Both drugs produced a statistically significant increase in the coefficient-value as compared to the placebo. The difference between the two drugs was not significant.

(*b*) *Outflow fraction*

Mean P_0/C value for cases on placebo 209·83.

Cases on pilocarpine 110·54 (S.E. 7·56) (full cases 102·0; non-placebo cases 170·5).

Cases on aceclidine 147·65 (S.E. 11·22) (full cases 123·38; non-placebo cases 188·90).

Percentage change from placebo to pilocarpine 54·13 per cent., that from placebo to aceclidine 41·16 per cent. Both drugs produced a statistically significant fall in the outflow fraction compared to the placebo. The difference between the two drugs was probably not significant. There was a rather large scatter in the figures.

(3) PUPIL DIAMETER

Mean diameter for cases on placebo 3·84 mm.

Cases on pilocarpine: overall mean 1·87 mm. (S.E. 0·09) (full cases 1·94 mm.; non-placebo cases 1·71 mm.).

Cases on aceclidine: overall mean 1·71 mm. (S.E. 0·09) (full cases 1·82 mm.; non-placebo cases 1·58 mm.).

Percentage reduction in pupil diameter from placebo to pilocarpine 47·84 per cent.; that from placebo to aceclidine 52·43 per cent. Both drugs produced significant miosis but the difference between the two was not significant.

(4) HYPERAEMIA

This was observed in 34 cases. It was more frequent with aceclidine than with pilocarpine.

Discussion

(1) INTRAOCULAR PRESSURE

In the present study, aceclidine was found to have a definite effect in lowering the intraocular pressure of eyes with open-angle glaucoma. This is in agreement with all the published work. The overall mean pressure in cases on aceclidine was 1·53 mm. Hg higher than that in cases on pilocarpine 2 per cent., a difference that is not statistically significant. The difference between the mean pressure produced by the two drugs was higher in the non-placebo cases (1·72 mm.) than in the full trial cases (1·36 mm.), suggesting that in patients with a high initial intraocular pressure (or a shallow anterior chamber) a stronger concentration of aceclidine might be necessary.

These results are similar to the results of the chronic experiments of Demailly (1968), in which the pressure in cases on pilocarpine was 19·1 mm. Hg, and that in cases on aceclidine was 20·2 mm. Hg. However, in his acute experiments, pilocarpine produced a percentage fall in pressure of 27 (± 12) compared to 30·6 (± 13·8) for aceclidine. Leopold (1968) found, in acute experiments in cases of chronic simple glaucoma, that 2 per cent. aceclidine salicylate had a greater action in lowering the intraocular pressure than pilocarpine 2 per cent. Étienne, Barut, and Gonzalès-Bouchon (1967), in twenty cases of chronic simple glaucoma, found a mean lowering of the intraocular pressure with aceclidine of 7·65 mm. Hg. Agugini and Stecchi (1968) reported no difference in the hypotensive action of the two drugs when the three daily readings over 3 days were averaged, although the figure for aceclidine (20·95 mm. Hg) was slightly lower than that for pilocarpine (22·29 mm. Hg). Brancato and Boschi (1968), comparing the action of the two drugs in ten subjects, found that aceclidine was "incomparably better", but gave no statistical evaluation.

(2) AQUEOUS OUTFLOW

It was this aspect of the effect of direct-acting parasympathomimetic miotics that appeared to be the most intriguing. In the present study, aceclidine was found to have a definite effect in improving the facility of outflow in eyes with open-angle glaucoma. The difference in the mean C-value of cases on pilocarpine and aceclidine was 0·01 (full trial trial cases difference = 0; non-placebo cases difference = 0·01). Lieberman and Leopold stated categorically that, so far as their work was concerned, aceclidine had no effect whatsoever on outflow facility (except in their chronic simple glaucoma suspects and secondary glaucoma cases), a unique property in a miotic. They observed a definite pressure-lowering effect, which led them to a most interesting theoretical discussion of how the drug produced this effect (see below). Demailly (1968), in his chronic and acute experiments, found that aceclidine produced a significant improvement in outflow but was no significant difference between the effects of pilocarpine 2 per cent. and aceclidine HCl 2 per cent. on the C-value or on P_0/C. However, the effect of aceclidine was consistently less powerful. A study, in the acute experiments, of the logarithm of the C-values, usually of a Gaussian distribution in normal subjects, revealed a significantly greater improvement with pilocarpine than with aceclidine. Among the other studies, Étienne and others (1967) found a highly significant improvement of outflow with aceclidine in cases of glaucoma simplex; the mean improvement in the C-value was 0·048. Riegel and Leydhecker (1967) observed an improvement in the C-value with aceclidine from a base line of 0·17 to 0·20, rather less than the 0·22 obtained with 2 per cent. pilocarpine. Gil del Rio (1968) found a mean increase of 0·051. Lepri and Tota (1967) observed an improvement in C-value of the order of 0·03. Brancato and Boschi (1968) observed an "identical" improvement in the C-value on both drugs. Magouritsas and Coliopoulos (in press) and Mazzilli and Mazza (1967) also observed a definite improvement in outflow.

Of all the published studies, therefore, only that of Lieberman and Leopold (1967) reports no improvement in outflow with aceclidine.

Mechanism of the effect of the two drugs

(*a*) It could conceivably be produced by a reduction of aqueous formation. Pilocarpine itself has been demonstrated to have an inhibitory effect on the ciliary process *in vitro* (Berggren, 1965). This effect has not been studied for aceclidine.

(*b*) Demailly, comparing the effect of the two drugs, explained the greater tension-lowering effect of aceclidine by the smaller amount of reactive hypersecretion which occurs after the use of both drugs. That this effect was indeed greater with pilocarpine was suggested by flow-studies, using both the results of tonography, with Goldmann's $F = (P_o - P_v)$ formula, and suction cup studies.

(*c*) Bárány (1962), experimenting on the monkey *Cercopithecus ethiops*, demonstrated that the increase in outflow facility produced by pilocarpine could be reversed by atropine in two stages, a fast and a slow. The fast stage lasted approximately as long as the accommodative spasm produced by pilocarpine, and could correspond to a facilitation of outflow produced by a pull of the ciliary muscle on the trabecular meshwork (and possibly on the endothelial cells of Schlemm's canal). The slow phase could correspond to the abolition of a histamine-like action of pilocarpine directly on the endothelial cells or a widening of the transendothelial channels (this latter phenomenon could not be confirmed in later experiments). In some individuals an increase in facility may be mainly due to the ciliary muscle pull, whereas in others it may predominantly correspond to the effect on the endothelium. It is possible that aceclidine lacks the latter effect (it produces intense miosis, so it is probably unlikely to be without effect on the ciliary muscle).

(*d*) Another explanation could be related to the recent concept of the uveo-scleral flow of aqueous along the interfascicular spaces of the ciliary body directly to the venous circulation (Bill and Bárány, 1966). Pilocarpine, possibly by causing ciliary spasm, is thought to close up this alternative pathway for aqueous outflow. The effect of aceclidine has not been studied and it could be weaker than that of pilocarpine.

(3) MIOSIS

In the present study, aceclidine was found to produce slightly more powerful miosis than pilocarpine.

Demailly (1968) obtained the impression that the miosis produced after one hour was greater with aceclidine than with pilocarpine, though the pupillary diameters were not measured. Gil del Rio (1968), using an electronic flash photographic method, noted early miosis with aceclidine, starting 4 minutes after instillation and reaching its maximum between 20 and 80 minutes. Étienne and others (1967) also noted "intense miosis". Rouher (1966) observed miosis after 30 minutes, maximal after 90 minutes, the pupil then being 47 per cent. of its original diameter. Riegal and Leydhecker (1967) noted a mean pupillary diameter on pilocarpine of 1·6 mm. and on aceclidine of 1·7 mm. This would appear to be the only study in which the miotic effect of pilocarpine was noted to be stronger than that of aceclidine.

(4) HYPERAEMIA

This was more frequent with aceclidine in the present study (Table IV, opposite). Demailly (1968) observed that it produced the same degree of congestion as pilocarpine. Riegel and Leydhecker (1967) observed only three cases of hyperaemia in 51 eyes, lasting only for 1 or 2 days.

(5) BROWACHE OR HEADACHE

This was noted in 23 cases (Table IV), and was more frequent with aceclidine. Itin and Ricci (1967) reported slight headache in four out of fifteen patients.

(6) SMARTING

This occurred in thirty cases, being approximately equal with the two drugs. It also occurred in four eyes on placebo drops (Table IV).

Table IV

Symptoms	*Absent*	*A > P*	*P > A*	*Equal*	*More with placebo*
Pain, browache	20* > 31 11**	7 > 12 5	4 > 6 2	3 > 5 2	—
Smarting	19 > 24 5	10 > 12 2	2 > 11 9	1 > 7 6	4 > 4 0
Hyperaemia	13 > 20 7	10 > 18 8	2 > 2 0	9 > 14 5	2 > 2 0
Watering	24 > 33 9	3 > 7 4	2 > 4 2	5 > 10 5	—
Rhinorrhoea	15 > 12 8	8 > 12 4	3 > 4 1	8 > 15 7	—
Sialorrhoea	30 > 49 19	0 > 0 0	1 > 1 0	3 > 4 1	+1

* refers to cases in the full trial
** refers to cases in the non-placebo trial

(7) BLURRING AND DARKENING OF VISION

These occurred in 38 and 28 cases respectively, being more frequently noted with aceclidine. In Demailly's experience accommodative myopia is the same as with pilocarpine. The only other reference in the published work to this symptom is that of Itin and Ricci (1967), who noted transient visual disturbances in four out of fifteen patients.

(8) SIALORRHOEA

This occurred in seven cases and was rather more frequent with pilocarpine than with aceclidine (Table IV). This is in contrast with the observations of Étienne and others (1967), who found that aceclidine produced no sialorrhoea in man as it did in animals.

(9) RHINORRHOEA

This occurred in 31 cases, more often with aceclidine than with pilocarpine (Table IV).

(10) SNEEZING

This occurred in eight cases: in four with aceclidine, one with pilocarpine, and three equally with both drugs. It also occurred in one case on placebo drops. The literature here is conflicting: Demailly (1968) reported no instance of sneezing following the instillation of aceclidine, whereas Étienne and others (1967) reported it in *all* patients.

(11) GASTROINTESTINAL DISTURBANCES

None was observed, and this finding is similar to that of other workers. Such disturbances are, in fact, seldom observed with pilocarpine but are frequent with carbachol, together with other manifestations of systemic intoxication.

Long-term tolerance of aceclidine

The following brief histories of patients outside the double-blind series are included as examples of good acceptance of aceclidine when pilocarpine was not tolerated.

(1) *Mrs. E. W.*

Irritation on pilocarpine with intolerable discomfort. Given aceclidine for 6 months. Quite comfortable on this therapy. Seen at 3-weekly intervals: ocular tension between 12 and 20 mm. Hg.

(2) *Mrs. W. P.*

Much irritation on pilocarpine. Given aceclidine for 19 months. Much less irritation, though more "darkening". Pressure during entire period between 20 and 22 mm. Hg (had been 32 mm. previously). On resuming pilocarpine the pressures were around 24 mm. Hg in each eye. Complained of pain around eyes and discharge. Eppy and eventually hydrocortisone drops necessary.

(3) *Mrs. D. B.*

Irritation on pilocarpine. Given aceclidine for 3 months. Initial comfort but slight discomfort for one month which passed off. Tension 23 to 27 mm. Hg on pilocarpine 2 per cent., and 21 to 24 mm. Hg on aceclidine. Resumed pilocarpine 3 per cent. and eserine 0·5 per cent. Gradually developed intense hyperaemia and discomfort. Local steroids attempted. Tosmilen eventually tried.

(4) *Mrs. T. P.*

Allergic to pilocarpine. Was receiving gutt. Betnesol. Given aceclidine for 12 months with excellent tolerance, much less discomfort, and much less congestion. With Eppy 1 per cent. in addition control was satisfactory. (Tensions 21 to 22 mm. Hg at all times.) When pilocarpine 2 per cent. was resumed the tensions were around 24 to 26 mm. Hg and she again complained of discomfort.

(5) *Mr. T. S.*

Sensitive to pilocarpine and eserine, and was given phospholine iodide with Eppy. The tensions were 24 to 26 mm. Hg. Given aceclidine with Eppy and seen monthly for a year. Much more comfortable. Pressures around 17 to 24 mm. Hg. When pilocarpine 3 per cent. was resumed absolute intolerance was complained of. Again given aceclidine and discomfort disappeared. When supplies of aceclidine were exhausted prostigmine (neostigmine) 3 per cent. was tried but caused a considerable burning sensation which was soothed to some extent by adrenaline.

Summary

The results of a double-blind cross-over comparison of aceclidine hydrochloride 2 per cent. and pilocarpine 2 per cent. in 54 glaucomatous eyes are presented. Both eye drops produced a significant lowering of intraocular pressure and improvement in outflow and in the degree of miosis, but the differences between the two were small and not significant. Hyperaemia and a variety of subjective symptoms were also compared: neither drug produced serious side-effects or discomfort. Aceclidine would appear to deserve a place

beside pilocarpine as a stable direct parasympathomimetic drug in the treatment of open-angle glaucoma, especially if pilocarpine is not tolerated, or if it is ineffective, or becomes so after a period of use.

My thanks are due to Messrs. Chibret, France, for generous supplies of aceclidine and assistance with the Continental literature, to Mr. Redmond J. H. Smith for his advice and encouragement, and to Mr. Baker, Chief Pharmacist, Moorfields Eye Hospital, for organizing the dispensing of random series of eye drops.

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Extruded collagen ophthalmic sutures

A clinical survey

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During the last decade ophthalmic surgeons have shown increasing interest in absorbable sutures, though a large body of opinion still favours silk and synthetic fibres. Hitherto, prejudice against catgut centred in the uncertainty of tissue reaction, wound healing, and absorption, and physical defects such as brittleness and unsuitable needles.

The change of outlook follows improved manufacturing processes resulting in stronger and finer catgut and needles more suitable for ophthalmic work. A substitute for catgut, Plain and Chromic Extruded Collagen*, has been made from the flexor tendons of cattle. These are digested and dispersed in an acid medium and homogenized. The collagen dispersion is then extruded to form a tape and multiple tapes are converted into round uniform strands of specified thickness and length and the needles are swaged on. The sutures are sealed in aluminium foil packets and sterilized by electron beam irradiation.

My 5 years' personal experience with catgut in cataract extractions has given convincing proof of the value of absorbable sutures in ophthalmic surgery. This paper reviews 151 cataract extractions and 155 squint operations in which, with the co-operation of the manufacturers, Extruded Collagen only was used in order to assess from a clinical point of view its physical and biological properties.

(1) In the first series only Plain Collagen was used, the sutures being 4/0 Plain double-armed Collagen with G3 cutting micro-point needle and 6/0 Plain double-armed Collagen with G6 cutting micro-point needle. The 4/0 Collagen was used only for sclero-muscular attachments in squint operations, and the 6/0 for corneo-scleral and conjunctival suturing. In the last ten cases of squint in this series 6/0 Collagen was used also for sclero-muscular suturing.

(2) In the second series only Chromic Collagen was used, namely, 6/0 Chromic double-armed Collagen with a G6 cutting micro-point needle in all cases throughout the series.

Surgical technique

(1) LENS EXTRACTION

Local anaesthesia was given in all cases. Cataract knife section incorporating a broad conjunctival flap was followed by peripheral iridectomy. Three pre-placed corneo-scleral sutures were inserted and the lens was removed with capsule forceps, erisophake, or cryoprobe. Zonulysin was not used. The wound was closed in three ways with 6/0 Collagen:

(*a*) Three interrupted corneo-scleral sutures were tied on the conjunctival surface, with the knots and cut ends exposed (Diagram A). This method was discontinued after the first six cases in the first series.

(*b*) The corneo-scleral sutures were placed subconjunctivally and the ends cut short. This was done in 44 cases of the first series and in all those in the second series (Diagram B).

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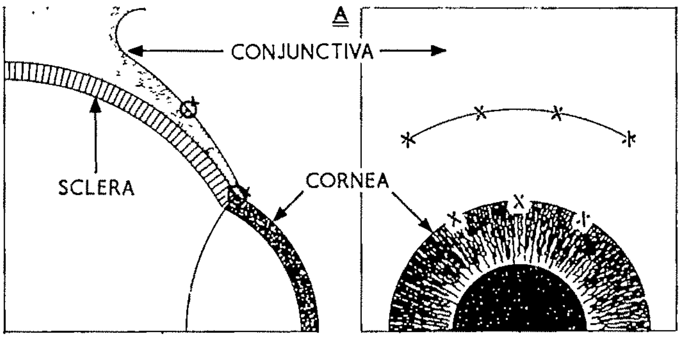
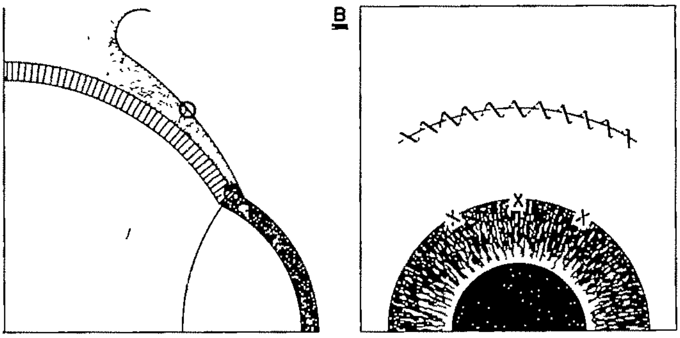
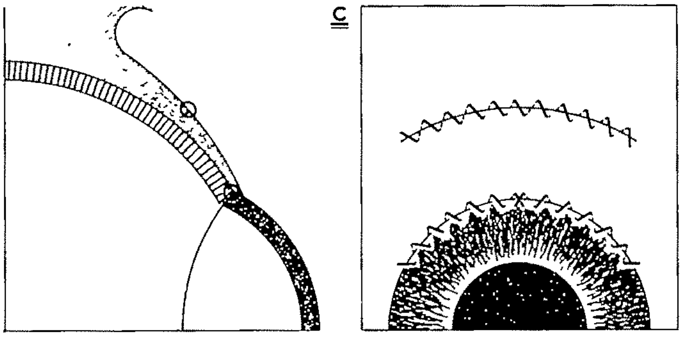
* Produced by the Ethicon Suture Company

(*c*) A double-armed corneo-scleral suture was inserted at 12 o'clock and tied beneath the conjunctiva, and the nasal and temporal extremities were used for continuous corneo-scleral suturing along their respective sections (Diagram C). This was done in twelve cases of the first series.







The conjunctiva was closed with a running suture in all cases after the first five, in which interrupted sutures were used.

(2) SQUINT OPERATIONS

General anaesthesia was given in all cases. In *recession* operations a Collagen Suture was placed at the upper and at the lower musculo-tendon extremity and a cinch suture tied with a single knot before section and suturing at the new insertion. In *resection* operations the suture was similarly placed in the upper and lower borders of the muscle at the appropriate distance from the insertion before section, and re-suturing was done at the original insertion. The running conjunctival suture was tied at each end, so completing the procedure, sealing off the operation area.

LIBRARY

Physical properties

SUTURE MATERIALS

Both Plain and Chromic Collagen had satisfactory pliability and tensile strength only when moist. Unless the Collagen was thoroughly soaked it quickly became wiry and brittle as the moisture evaporated through use. Chromic Collagen retained moisture longer and in consequence its pliability and strength lasted longer. Therefore, long loops and loose ends of the pre-placed sutures were moistened frequently along their length throughout operation.

Smooth passage through the sclera and cornea was facilitated by the fact that the Collagen did not fray as catgut often does, and also by the uniformity of its gauge. Unlike catgut, the material did not stretch and the knots held firmly, allowing the free ends to be cut very short. This reduced the bulk of the suture beneath the conjunctiva, especially with the 4/0 suture. The 6/0 suture knots were very small and unobtrusive.

The Chromic Collagen seemed more pliable and the exposed cut ends caused less mechanical irritation than those of Plain Collagen. The main reason for using running conjunctival sutures and subconjunctival corneo-scleral sutures was to reduce this discomfort.

The 6/0 suture was at first thought to be too fine for squint surgery, but it proved to be very suitable for sclero-muscular sutures, provided it was kept well moistened throughout the operation and not exposed to sudden uneven tension when tying knots.

NEEDLES

The G6 needle with the cutting micro-point was ideally suited for corneo-scleral work—its sharp point with cutting edge and its suitable size and curvature allowed smooth passage of the needle with minimum trauma. Care had to be taken, however, to avoid tilting the needle while passing through sclera, as this might have caused the encroaching edge to cut through. I found the slightly larger G3 needle with the 4/0 suture very satisfactory. Numerous types of needle holder were tried, but the problem of the swivelling of the needle was never satisfactorily resolved.

Biological properties

CATARACT EXTRACTION. SERIES I

This comprised sixty intracapsular cataract extractions in which 6/0 Plain Collagen only was used.

Tissue reaction

(1) *Conjunctival suture*

(a) The interrupted sutures were surrounded by a small localized patch of oedema lasting 2 to 5 days and associated with conjunctival congestion which took 3 to 4 days longer to subside. This effect was accentuated by irritation from the projecting cut ends of the sutures, which caused pain and lacrimation during the first 24 to 36 hours. For this reason the use of interrupted conjunctival sutures was discontinued.

(b) A running conjunctival suture was used in all subsequent cases. Slight oedema and congestion appeared at the overlaps, especially when it was drawn tight, by the 2nd day, but this rapidly subsided. There was no discomfort.

(2) *Corneo-scleral suture*

(a) The exposed interrupted suture tied on the conjunctival surface caused discomfort and increased injection of the eyeball and lids from mechanical irritation of the knots during the first 2 days. Therefore, after the first six cases, all sutures were placed subconjunctivally.

(b) The subconjunctival sutures caused only slight reaction with no oedema, except in two cases in which erosion occurred.

(c) The continuous corneo-scleral subconjunctival suture produced slight local oedema and congestion which subsided in 7 to 10 days. Vascular proliferation and congestion in and around the corneo-scleral section was never excessive; it reached its maximum intensity by the 5th day and in many cases faded rapidly by the 8th to 9th day.

Wound healing

This was firm and was not delayed except in three cases in which the sutures were slack allowing slight gaping between them. The continuous corneo-scleral suture was followed by speedy and firm union especially if tied at each extremity to prevent slackening. In this series no iris prolapse occurred.

Period of absorption

The running *conjunctival suture* absorbed evenly within 7 to 12 days; the interrupted single sutures took longer, up to 21 days in some cases, especially if the ends were long.

The exposed interrupted *corneo-scleral sutures* absorbed slowly in 4 to 6 weeks, but when they were placed subconjunctivally absorption was speeded up to a period of 2 to 3 weeks depending on the size of the knot and the length of the cut ends. Erosion occurred in two cases, increasing the absorption time by 7 to 10 days.

Complications

There were no complications that could be directly attributable to the Collagen. There were three cases of residual hyphaema following haemorrhage into the anterior chamber during the operation but no postoperative hyphaemata. Striate keratitis along the edge of the corneal section occurred in two cases.

CATARACT EXTRACTION. SERIES 2

This comprised 91 cataract extractions in which 6/0 Chromic Collagen only was used.

Tissue reaction

Chromic Collagen differed slightly from Plain Collagen, chiefly in the remarkably low degree of reaction and the more rapid absorption of the conjunctival sutures.

Initial reaction was minimal at 48 hours, when the first dressing was done. There was no oedema around the sutures; this was in marked contrast to the Plain Collagen.

Later superficial and deep conjunctival congestion increased until the 5th day and then rapidly subsided. The subconjunctival corneo-scleral knots projected slightly beneath the conjunctiva, but deep local reaction around them was slight. By the 9th to the 12th day the eyes were quiet; in many cases the eyes were white by the 6th day.

Erosion of the corneo-scleral knots occurred in four patients which delayed absorption by 1 to 2 weeks. This was not accompanied by increased local inflammation or by a weakened corneo-scleral scar.

Wound healing

Close apposition of the corneo-scleral wound edge was occasionally defective midway between the three corneo-scleral sutures, especially if they were slack, and in three cases iris prolapse occurred at this site. Safe and firm union was obtained by a corneo-scleral bite of two-thirds depth at right angles to the sclera; oblique suturing caused distortion and defective union. An increased number of sutures would eliminate this defect and, in view of the low incidence of reaction, additional sutures are unlikely to increase discomfort. Throughout postoperative convalescence the patients complained of no discomfort other than slight soreness during the first 24 hours.

Period of absorption

This was much the same as with Plain Collagen though slightly shorter, namely 6 to 9 days for the conjunctival suture and slightly longer for the corneo-scleral subconjunctival sutures, namely 3 to 5 weeks depending on the size of the knots and cut ends.

Postoperative complications

There were three cases of striate keratitis and two of postoperative hyphaema. This may have been indirectly associated with the Collagen but is as likely to occur with other suture materials.

Postoperative visual results

These are not influenced directly by the choice of suture material, other factors being of greater significance, but firm accurate apposition of the corneo-scleral wound edges by subconjunctival sutures reduces the incidence of postoperative astigmatism. From a random selection of 55 cases in this series, the astigmatism is listed as follows:

+ 0·5 to + 1·5	15 cases
+ 2·0	16 cases
+ 2·5	12 cases
+ 3·0 to + 3·5	9 cases
+ 4·0	3 cases

SQUINT OPERATIONS. SERIES I

In this consecutive series of 100 cases, Plain Collagen only was used. 6/0 sutures with the G6 cutting micro-point needle were used for the conjunctiva and also for the sclero-muscular suturing in the last ten cases. 4/0 sutures were used for sclero-muscular suturing in the first ninety cases.

Reaction

This was slight, but oedema around the conjunctival sutures was evident at the first dressing. This subsided within 2 days and the accompanying conjunctival congestion subsided within a week. In six cases, however, severe and deep-seated oedema and congestion occurred over the site of one buried sclero-muscular suture. This was accompanied by pain on moving the eye and, in three patients, by pyrexia which responded rapidly to local steroids and systemic antibiotics. In two patients the deep localized reaction recurred at the same site after an interval of 6 to 8 weeks. Despite this reaction no granulomata were observed. In the ten cases in which 6/0 Collagen was used, the reaction was negligible.

SQUINT OPERATIONS. SERIES 2

In this series of 55 cases, 6/0 Chromic Collagen with the G6 needle was used for sclero-muscular as well as conjunctival suturing.

Reaction

No oedema was seen around the conjunctival sutures, and conjunctival congestion, though noticeable in the first 4 days, rapidly subsided, the eye becoming quiet by the 6th to 7th day. This reaction was severe in only two cases in which it was associated with deep sclero-muscular inflammation. This responded rapidly to local steroids and systemic antibiotics. The late appearance of a granuloma occurred in three cases. All patients were allowed home on the 1st or 2nd day after the operation.

Absorption

As in the first series, the conjunctival sutures absorbed in 7 to 9 days. It was not possible to assess the period of absorption of the sclero-muscular sutures. The absence of discomfort from the 2nd day in most cases suggests a negligible reaction at the suture site. Subsequent favourable orthoptic measurements confirmed my opinion that these 6/0 Collagen sutures hold the new insertion effectively and are very suitable for squint surgery.

Comments

Previous experience with catgut encouraged this survey, which demonstrated the suitability of absorbable collagen sutures in ophthalmic surgery. Absorbable sutures eliminate the unnecessary discomfort and risk of ocular trauma entailed in the removal of non-absorbable sutures and cause less reaction.

The advantages of the G6 needle in both corneo-scleral and sclero-muscular suturing was demonstrated in all cases—adequate fixation by a suitable needle holder is desirable.

The 6/0 Chromic Collagen has proved to be a satisfactory material in both corneo-scleral and sclero-muscular suturing, provided it is kept moist throughout the operation. Under these conditions it is very pliable and has greater tensile strength than ordinary catgut, and the knots hold firmly however short the cut ends may be.

The period of absorption is not too rapid; adequate union takes place during the post-operative period.

Absence of reaction ensured greater comfort and the patients were fit for discharge much earlier than hitherto—many of our cataract patients are now discharged on the 6th day, some even on the 5th. This applies also to squint patients who are discharged on the 1st or 2nd day after operation.

The use of multiple subconjunctival corneo-scleral sutures in cataract patients reduces postoperative astigmatism and has a favourable influence on postoperative visual acuity.

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Corneal stromal overgrowth after cataract extraction

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Corneal stromal overgrowth (retrocorneal membrane, fibrous overgrowth) is one of the common complications of penetrating keratoplasty (Kurz and D'Amico, 1968). As a postoperative complication of cataract extraction leading to enucleation, however, it is less well recognized. Few case reports exist in the literature, and Duke-Elder (1969) fails to cite stromal overgrowth as a complication of cataract extraction. Two striking examples of stromal overgrowth after cataract extraction will be reported: one after intracapsular and one after extracapsular surgery.

Case reports

Case 1, a 75-year-old female, had a cataract extracted from the left eye in April, 1969. A peripheral iridectomy was performed and the lens was delivered intracapsularly. No note of vitreous loss or other complication was made at time of surgery. An iris prolapse with shallowing of the anterior chamber developed postoperatively. One week after the cataract extraction the patient had a sector iridectomy with reformation of the anterior chamber. She developed bullous keratopathy and secondary glaucoma, and medical management was instituted without success. Cyclodiathermy was performed in August and again in September, 1969. The ocular tension was not controlled and the eye was enucleated in November, 1969.

The specimen consisted of an intact, firm left eye measuring 24 × 23·5 × 24·5 mm. with scant attached optic nerve. The cornea, which measured 11 × 11 mm., showed bullous keratopathy, and its stroma was diffusely hazy. Superiorly a retrocorneal membrane was present. A sector iridectomy and inferior sphincterotomy was seen. The globe was opened in the vertical meridian, and the lens was absent. Peripheral anterior synechiae occluded the anterior chamber angle. Focal areas of depigmentation surrounded by hyperpigmentation were present in the pars plana inferiorly.

MICROSCOPICAL EXAMINATION

The subconjunctival tissue shows a mild, round cell infiltration. The corneal epithelium is thinned focally, but is intact. Several large epithelial bullae are present. Bowman's membrane has scattered defects. A fibrovascular membrane, most marked near the limbus, lies between the basement membrane of the epithelium and Bowman's membrane. A vascularized surgical scar extends from behind the limbus, continues almost parallel to the plane of the cornea, and enters the anterior chamber anterior to Schwalbe's line (Fig. 1). Uveal pigment is present within the vascularized scar. The remainder of the stroma shows deep vascularization and round cell infiltration. Descemet's membrane is thickened, irregular, and broadly interrupted at the inner aspect of the scar.

Through this interruption a large stromal overgrowth or retrocorneal membrane is present (Fig. 2).

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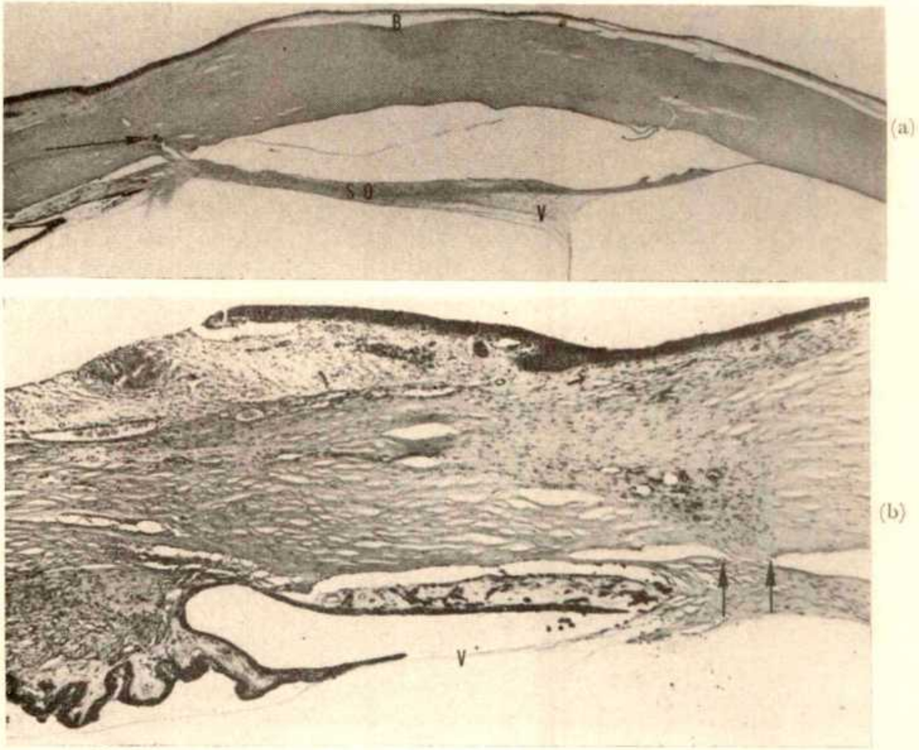

FIG. 1 *Case* 1

(A) Low-power photomicrograph, showing stromal overgrowth (SO), vitreous (V), and subepithelial bulla (B). Track of surgical incision delineated by arrow. Haematoxylin and eosin. ×15

(B) Higher-power view of stromal overgrowth, showing dehiscence in Descemet's membrane (between arrows) and a vitreous strand (V). Haematoxylin and eosin. ×30

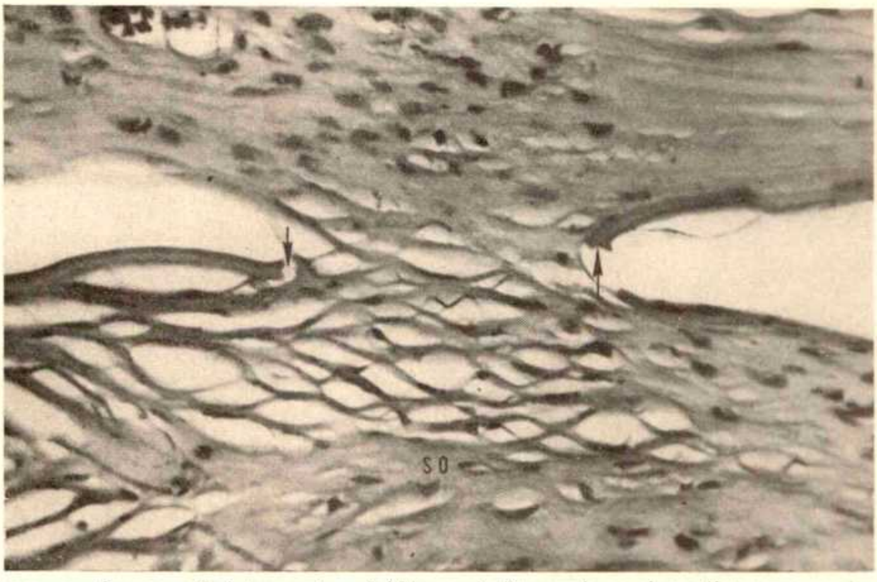

FIG. 2 *Case* 1. *High-power view of dehiscence in Descemet's membrane (between arrows) and stromal overgrowth (SO). Cornea with iris pigment is seen above. Haematoxylin and eosin.* ×240

It attaches, on one side, to the remnant of iris and to the vitreous (Fig. 1). This overgrowth continues toward the opposite limbus along the cornea, from which it is artificially separated. The anterior chamber angle is closed by peripheral anterior synechiae. Hyalinization of the sphincter muscle and degeneration of the dilator muscle are present in the iris. Ciliary processes are hyalinized. On the side with the iridectomy the most anterior ciliary process is pulled towards the wound by a vascularized strand. The retina shows peripheral cystoid degeneration. In the periphery on the inferior side chorio-retinal adhesions are present. Here the retina is degenerated; the retinal pigment epithelium is absent; focal pigment clumps are present; and the cortical vitreous is applied to the internal limiting membrane. Ganglion cells are absent and the nerve fibre layer is degenerated. Myelin artefact is present beneath the retina on one side of the optic nerve. On the other side there is a flat retinal detachment with subretinal fluid. The optic nerve shows cupping, atrophy of fibres, and glial proliferation. The vitreous is collapsed.

Case 2, a 60-year-old male, had a cataract extraction of the right eye in November, 1967. The history is incomplete but the extraction was extracapsular, and the postoperative course was complicated by the development of intractable secondary glaucoma; 9 months later the blind painful eye was enucleated.

The specimen consisted of an intact, firm, shrunken right eye measuring 22 × 20 × 20 mm. with 6 mm. of attached optic nerve. The cornea was opaque. The globe was opened vertically. The lens was absent.

MICROSCOPICAL EXAMINATION

The corneal epithelium is thin and Bowman's membrane has been largely replaced by degenerative pannus. Corneal stroma shows deep and superficial vascularization. A large defect is present in Descemet's membrane near the limbus (Fig. 3). Through the defect a large stromal overgrowth has developed (Fig. 4). The fibrous tissue fills the angle on this side, extends along the posterior surface of the cornea, and is present in the opposite angle. Descemet's membrane is reduplicated near the dehiscence. Peripheral anterior synechiae occlude the angle. The iris stump, angle structures, and ciliary body are infiltrated by chronic inflammatory cells. Fragments of lens capsule and sub-

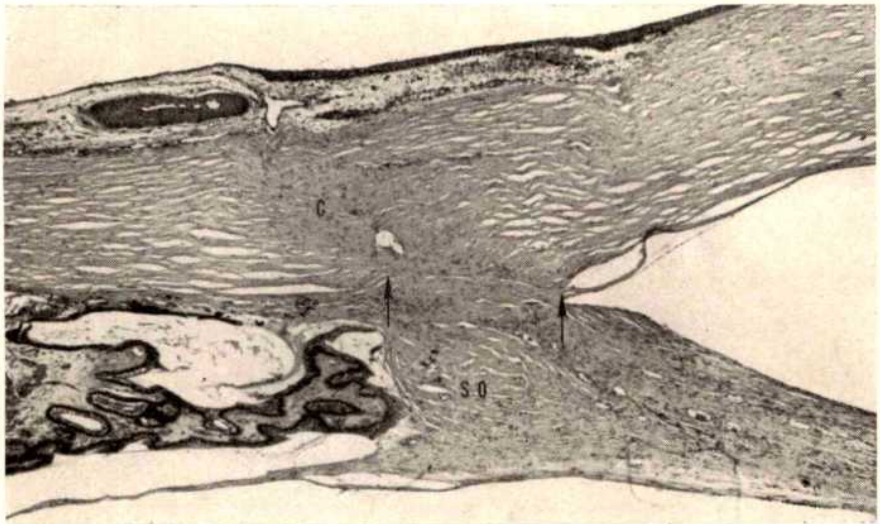

FIG. 3 *Case 2. Low-power view, showing corneal cicatrix (C), dehiscence in Descemet's membrane (between arrows), and stromal overgrowth (SO). Haematoxylin and eosin.* ×30

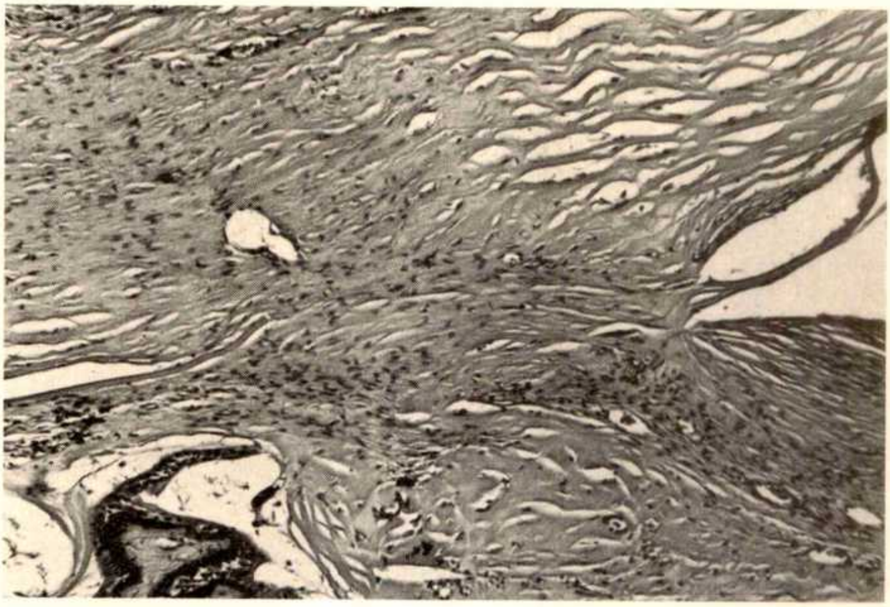

FIG. 4 *Case 2. Higher-power view, showing defect and stromal overgrowth. Ciliary processes are seen on the left. Haematoxylin and eosin.* ×75

capsular epithelium lie in the pupil and are applied to the retrocorneal membrane. A vascularized cyclitic membrane incorporates the vitreous and the totally detached retina. Posteriorly a serous exudate lies beneath the retina. The optic nerve is atrophic and myelin extrusion is present in the nerve head.

Comment

Normal corneal wound healing after cataract extraction follows a definite pattern (Dunnington, 1956). Primary closure of the corneal incision is due to swelling of the corneal lamellae, mostly as a result of imbibition of aqueous. Within 3 or 4 days fibroblastic proliferation commences and stromal healing begins. Early in the reparative phase the anterior and posterior edges of the wound retract. The epithelial integrity is restored by a slide from the wound edges and by proliferation. During this period epithelium may extend along and under the incisional tract. The anterior triangle of epithelium is gradually expelled by the proliferation of fibroblasts. Descemet's membrane is retractile and will form folds and scrolls. The posterior wound gape is repaired later after stromal proliferation is well established. Endothelium proliferates and bridges the defect.

Henderson (1907, 1914), studying Fuchs's cases of faulty wound apposition, noted proliferation of connective tissue into the anterior chamber. He thought this to be due to the presence of incarcerated iris, lens debris, or lens capsule within the wound acting as a bridge and allowing subconjunctival tissue entry into the anterior chamber. A fibrotic mass could then form in the angle and upper part of the anterior chamber leading to closure of the filtration angle with secondary glaucoma. Collins (1914) did not accept Henderson's thesis and suggested that proliferation of connective tissue was not possible without the presence of infective material. Swan (1951) attributed the fibroplasia to scleral reaction in the presence of lens matter, fibrin, or vitreous incarcerated in the wound.

Levkoieva (1947) and Duke-Elder (1954) described corneal stromal overgrowth as brought about by the exuberant proliferation of connective tissue into a gaping wound; this connective tissue was histologically identical to and arises from corneal stroma. Both these authors stated that the irritating influence of incarcerated ocular tissue and ocular fluids was necessary for the production of stromal overgrowth. Christensen (1965) pointed out that contact between intraocular structures and wound surfaces might provoke a chronic inflammatory reaction. This produced a prolonged reparative phase and subsequent excessive intraocular fibrocytic reaction. Formed vitreous being irritating in the corneal wound, its presence would promote fibroplasia. In this regard Blodi (1965) noted a lower incidence of corneal stromal overgrowth after extracapsular extraction, in which, presumably, the vitreous face was not in contact with the wound. Also the presence of vitreous within the wound would provide a bridge for entry into and proliferation within the eye of a fibrocytic membrane.

Thus three elements are necessary for stromal overgrowth:

(1) Posterior gaping or over-riding of the wound;

(2) Incarceration of vitreous, lens material, or iris in the wound;

(3) Inflammation within the eye.

In a case reported by Wood (1932), the stromal overgrowth was associated with marked iridocyclitis. In our cases contributory factors in the production of stromal overgrowth were:

(1) Anterior placement and marked bevelling of the incision, mimicking keratoplasty (Case 1);

(2) Postoperative iris prolapse and flat chamber which permitted posterior gaping of the wound for at least 1 week (Case 1);

(3) Iris incarceration in the wound (Cases 1 and 2);

(4) Vitreous incarceration in the wound as evidenced by adhesion between the vitreous face and the retrocorneal membrane (Cases 1 and 2);

(5) Postoperative inflammation (Cases 1 and 2).

Leading ophthalmic pathology textbooks (Hogan and Zimmerman, 1962; von Hippel, 1928; Parsons, 1904) do not mention corneal stromal overgrowth as a complication of cataract extraction. Duke-Elder, in an earlier work (1954), discussed stromal overgrowth following trauma; he cited the case of Wood (1932) as following cataract extraction, but did not include it in a long list of cataract complications in his more recent work (1969). Treatises on cataract surgery and its complications (for example, Kirby, 1950; McDonald, 1965; Stallard, 1965; de St Martin, 1935) also fail to list corneal stromal overgrowth. In six reported series, eyes enucleated after cataract extraction were studied histologically. These results are summarized in the Table (opposite).

Payne, Simonton, and Cury (1955) reviewed 333 and Schulze and Duke (1965) 100 globes removed after cataract extraction and did not mention corneal stromal overgrowth as a cause for enucleation. Blodi (1965) noted 251 eyes enucleated after cataract extraction; stromal overgrowth was responsible for five cases, four after intracapsular and one

Table *Corneal stromal overgrowth in eyes enucleated after cataract extraction*

Author	*Date*	*No. of eyes*	*Corneal stromal overgrowth*	*Epithelial downgrowth*
Payne and others	1955	333	0	60
Dunnington	1955	171	56	62
Blodi	1965	251	5	63
Schulze and Duke	1965	100	0	17
Allen	1968	50	18	13
Bettman	1969	74	25	5

after extracapsular extraction. Dunnington (1956) noted that, of 297 globes removed after cataract extraction between 1929 and 1954, 171 were due to faulty wound healing, and stromal proliferation was responsible for 56 of these. No mention was made of the ratio of intracapsular to extracapsular extractions. The enucleation often followed loss of vitreous and incarceration of tissue in the wound, and large amounts of lens cortex and capsule were frequently found adjacent to the wound. Allen (1968) studied stromal and epithelial ingrowths in fifty eyes removed after cataract extraction, stromal overgrowth was found in eighteen and epithelial downgrowth in thirteen. Bettman (1969) studied 74 eyes removed after cataract extraction; stromal overgrowth was found in 21 of 61 eyes removed after intracapsular extraction and in four of thirteen removed after extracapsular extraction. Bettman noted the frequent association of a stripped Descemet's membrane with stromal overgrowth.

The clinical recognition of corneal stromal overgrowth and its differentiation from epithelial downgrowth has been discussed by Swan (1951). The features of an epithelial downgrowth are an irregularly scalloped border, semitransparency, and a smooth regular surface. If unchecked, the epithelium will grow down along the corneal endothelium into the angle, and over the iris, ciliary body, and vitreous. Stromal overgrowths characteristically develop in areas where endothelium has been injured and Descemet's membrane stripped or gaping. The fibrous tissue will grow on the surface or invade the vitreous. The appearance of stroma differs from epithelium. Fibrous tissue is grey or white and Swan likened the appearance of the interlacing meshwork of fibres to that of woven cloth. In addition, the edges of the stromal overgrowth are frayed because of the penetration ahead of the fibroblastic strands. Considering that a stromal overgrowth is composed of actively developing fibroblastic tissue, radiation therapy may be helpful in arresting its development, and surgical intervention may be necessary.

Summary

Two examples are reported of corneal stromal overgrowth after cataract extraction. In one case the overgrowth followed intracapsular and in the other extracapsular extraction. The mechanism of its development and its clinical recognition are discussed. Previous studies noting the incidence of corneal stromal overgrowth after cataract extraction are summarized.

We wish to thank Mrs. Doris Ortega for secretarial work and Mr. Henrick Malpica for the illustrations.

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Proliferative diabetic retinopathy

Regression of optic disc neovascularization after retinal photocoagulation

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Photocoagulation is an accepted method of local treatment for proliferative diabetic retinopathy. It has been shown that 73·25 per cent. of eyes with proliferative diabetic retinopathy have new vessels on the optic disc at the initial visit (Taylor and Dobree, 1970). These vessels cannot be treated directly by photocoagulation. Aiello, Beetham, Balodimos, Chazan, and Bradley (1969) treated all grades of proliferative diabetic retinopathy by multiple choroido-retinal burns using the ruby laser, and in a preliminary communication they reported regression of optic disc neovascularization in some cases.

The purpose of this paper is to report the regression of new vessels on the optic disc after extensive retinal photocoagulation.

Clinical material and method

The present series (consisting of 31 eyes in 25 patients) was taken from a larger group of patients, all of whom have proliferative diabetic retinopathy, and are under regular ophthalmoscopic and photographic review.

The cases selected for review all fulfilled the following criteria:

(1) There was neovascularization associated both with the retinal veins and with the vessels on the optic disc.

(2) The areas of neovascularization associated with the retinal veins had been treated by photocoagulation at one or more sessions.

(3) The number of choroido-retinal burns had been recorded on each occasion so that the total number of coagulations given was known.

(4) There were complete preoperative and postoperative fundus photographic records.

The preoperative and postoperative photographs were used to compare the disc neovascularization before and after retinal photocoagulation. The vessels on the optic disc were assessed in respect of:

(*a*) Area.

(*b*) Total number of vessels crossing the disc margin.

(*c*) Absence or presence of supporting fibrous tissue, *i.e.* Stage I or Stage II (Dobree, 1964).

(*d*) Whether the neovascularization was flat or elevated *i.e.* lay immediately in front of the disc and retina or anterior to the retina by at least ¼ disc diameter.

The Zeiss photocoagulator was used in all cases, usually with a light intensity setting of Green II and an aperture of 4·5° giving a 1·35 mm. choroido-retinal burn. In the two exceptions, namely Eyes 10 and 22 (Table I), an aperture of 3·0° was selected to give a smaller burn to some areas with

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a greater light intensity of Green III. The smaller area was selected to give multiple scattered burns, as well as directly treating groups of new vessels associated with the retinal veins in the usual manner. Photocoagulation was carried out in one to four sessions, the maximum interval between treatments in any case being 7 months. The number of coagulations given was recorded automatically using the electronic coagulation counter (Dobree, Gaye, and Wiggins) at each treatment session, so the total number of burns given to each eye was known. The follow-up period varied from 2 to 24 months.

Results (Table I, opposite)

Retinal new vessels were treated by photocoagulation in 31 eyes, and in five eyes regression of the new vessels on the optic disc resulted (Figs 1 and 2). In two of these five eyes, there were no residual new vessels on the disc, and in the other three the new vessels were reduced in number and appeared more tenuous. Of the remaining 26 eyes, twelve showed no change in the appearance of the proliferation on the optic disc, and fourteen showed marked progression of proliferation with increase in the new vessels and fibrous tissue on the disc.

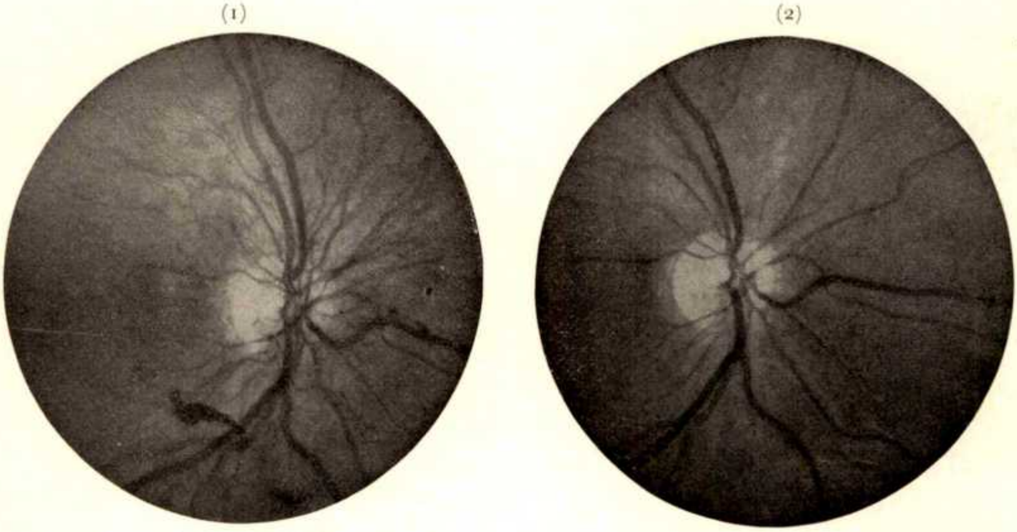
(1) (2)

FIG. 1 *Eye 19, before retinal photocoagulation*

FIG. 2 *Eye 19, 3 months after retinal photocoagulation showing regression of the new vessels on the optic disc*

Two aspects of these results call for more detailed examination with regard to their relationship to the subsequent changes in the disc vessels: the type of neovascularization present on the optic disc before treatment and the total number of coagulations given.

Table II shows that the only category in which regression of optic disc neovascularization occurred was that in which the new vessels were flat and unsupported by visible fibrous tissue. In the remaining categories regression did not occur.

The total number of coagulations given varied from 18 to 250, which is a very wide range. Ten eyes received over 100 coagulations. The eyes showing regression of optic disc new vessels had 250, 114, 136, 236, and 102 coagulations respectively. Assuming that there is no overlap of coagulation burns and knowing the number of burns with both 4·5° and 3·0° apertures, these eyes had 209·170 sq. mm., 163·202 sq. mm., 194·698 sq. mm.,

Table I *Details of disc neovascularization and total number of retinal photocoagulation burns in relation to subsequent disc neovascularization changes*

Patient no.	Eye	*Neovascularization of optic disc*		*Photocoagulation*		*Optic disc neovascularization after treatment*
		Stage I or II	*Flat or elevated*	*Number of sessions*	*Total number*	
1	R	II	Elevated	1	12	No change
2	R	II	Elevated	3	83	Progressed
3	R	I	Elevated	1	60	No change
4	R	I	Flat	2	61	Progressed
5	L	II	Elevated	2	54	No change
6	R	II	Elevated	4	196	No change
7	R	I	Flat	1	66	No change
8	R	II	Elevated	2	49	No change
9	R	I	Flat	2	66	No change
10	L	I	Flat	3	250	Regressed
11	L	II	Elevated	1	18	No change
12	L	II	Elevated	2	172	Progressed
13	L	I	Flat	1	47	No change
14	R	II	Elevated	4	68	Progressed
	L	II	Elevated	2	81	Progressed
15	L	II	Elevated	2	59	Progressed
16	R	II	Elevated	2	28	Progressed
17	R	II	Flat	2	142	Progressed
18	R	II	Elevated	1	49	Progressed
	L	I	Elevated	3	139	Progressed
19	R	I	Flat	3	114	Regressed
	L	I	Flat	2	136	Regressed
20	R	II	Elevated	3	103	Progressed
	L	II	Elevated	2	93	Progressed
21	R	I	Flat	2	31	No change
	L	I	Flat	3	79	No change
22	L	I	Flat	3	236	Regressed
23	L	II	Elevated	1	40	No change
24	R	I	Flat	1	92	Progressed
25	R	I	Flat	1	36	Progressed
	L	I	Flat	2	102	Regressed

Table II *Results of treatment in the four preoperative categories of disc neovascularization*

Disc neovascularization	*No. of eyes showing:*		
	Regression	*No change*	*Progression*
Stage I Flat	5	5	3
Elevated	–	1	1
II Flat	–	–	1
Elevated	–	6	9

158·110 sq. mm., and 146·023 sq. mm. of retina destroyed. The minimum area of choroido-retinal damage which was associated with regression of new vessels on the disc was 146·023 sq. mm. This is approximately 14 per cent. of the total retinal area.*

Discussion

Spontaneous regression of small areas of retinal neovascularization is well documented by those who have studied the natural history of proliferative diabetic retinopathy (Larsen, 1960; Dobree, 1964; Davis, 1967). It was also reported by Dollery and Oakley (1965) that retinal neovascularization in a diabetic might be completely reversible with improvement in diabetic control, but they were referring to dilated retinal hairpin capillary loops. Spontaneous regression of new vessels on the optic disc is not recorded.

Aiello and others (1969), after treatment of proliferative diabetic retinopathy by multiple laser burns to the retina, found regression of disc vessels in 26 out of 36 eyes with "early disc neovascularization". In eleven of these 26 eyes there were no residual new vessels visible clinically. In contrast, in those eyes where the disc neovascularization was advanced and elevated the response to laser coagulation was poor. In our series, five eyes showed regression of new vessels on the optic disc, and I would agree with Aiello that this favourable response is obtained in those eyes with early, flat neovascularization. Moreover, Okun and Johnston (1969) documented regression in one case of new formed vessels some distance from zones of photocoagulation and from the accompanying photographs it would seem that the disc vessels were flat and without visible fibrous tissue support before treatment.

The exact mechanism causing regression of new vessels is unknown, but the theory favoured by Aiello and others (1969) is that the multiple choroido-retinal scars reduce the metabolic requirements of the retina. They usually give 600 to 800 burns with a diameter of 0·75 mm. and Okun and Johnston (1969) give 100 to 300 burns with a diameter of 1·35 mm., so that the areas of retinal scarring are comparable to those in our series. It is reasonable to suppose that as results become available from other centres they may also show that regression of early disc neovascularization is dependant on the extent of the choroido-retinal burns, by either laser or light coagulation. It may even be possible to show that this regression follows a critical area of retinal destruction.

Summary

Neovascularization on the optic disc was studied in 31 eyes before and after retinal photocoagulation. There was regression of the new vessels on the optic disc in five eyes. The significance of the stage of disc neovascularization and the area of choroido-retinal scarring from photocoagulation is discussed.

I wish to thank Mr. J. H. Dobree both for permission to study these patients under his care and for his helpful advice. I also wish to thank Dr. Alan Jennings for his mathematical assistance and Miss Christine Otway for secretarial help.

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* I could find no reference to total retinal area. Duke-Elder and Wybar (1961) give the measurements for the diameter of the globe, the diameter of the cornea, and the position of the ora serrata in each quadrant in an emmetropic eye. A calculation based on these measurements gave an approximate retinal area of 1,050 sq. mm.

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Acute bacterial conjunctivitis in Assiout,* Upper Egypt

A one-year study

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Conjunctivitis is the commonest eye disease in Egypt, where it presents a major problem of public health. The chief menace of acute infective conjunctivitis lies in the corneal complications which may cause blindness. Since the late 1930s, the gonococcus and Koch-Weeks bacillus have been regarded as the most common causes of this condition in Egypt (Wilson, 1935; Lyons and Amies, 1949), but other organisms, such as pneumococci, streptococci, staphylococci, and *Moraxella*, may also be involved.

Most investigations of the problem in Egypt have been carried out near Cairo and Giza, but there are differences in climatic and social conditions between Upper and Lower Egypt, and this study has been made at the eye clinic of Assiout University in Upper Egypt.

This paper presents the results of a one-year bacteriological and epidemiological study.

Material

In the year 1967, a total of 28,872 patients was seen. The average number per month at each season and the average number of cases of conjunctivitis per month at each season are shown in Table I and Fig. 1. Conjunctivitis occurred most often in the Spring and Autumn; Summer came next and Winter last. A series of 320 patients from Assiout City and the surrounding villages was selected for study.

Table I *Average number per month of cases of acute conjunctivitis related to average number per month of all patients at each season*

Season		*Winter*	*Spring*	*Summer*	*Autumn*
Patients per month		1590	2300	3200	3100
Patients with conjunctivitis per month	No.	500	1500	1087	1574
	Per cent.	31 5	65	34	51

Methods

Each patient was given a thorough clinical examination and a sample of the conjunctival discharge was taken from each eye using a sterile platinum loop. The samples were immediately cultured on blood agar plates, and incubated at 37°C. for 48 hours to allow the slowly-growing bacteria to develop. Direct culture was more efficient than Gram-stained smears in detecting ocular bacteria of all types.

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* Assiout city (375 km. from Cairo) is the capital of Upper Egypt, where one of Egypt's new medical schools is established.

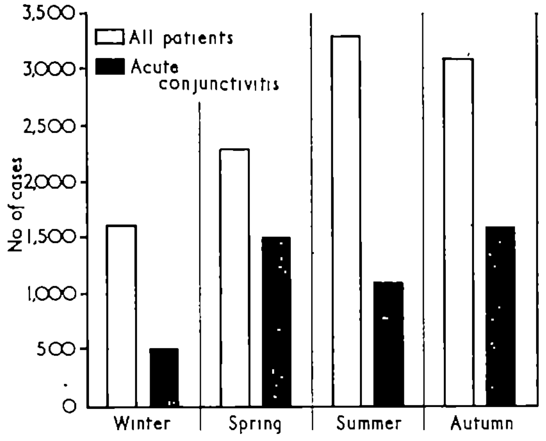

FIG. 1 *Average monthly number of cases of acute conjunctivitis related to average number of all patients*

Several strains of each organism isolated were tested for sensitivity to various antibiotics and chemotherapeutic agents.

Results

CULTURES (Table II)

In 189 of the 320 cases, ocular pathogens were isolated, in 126 cases only normal ocular flora were found, and in five cases the culture was negative.

Table II *Cultures of pathogenic bacteria and normal flora*

Result of culture		*Pathogens alone*	*Normal flora*	*Mixed*	*Negative*	*Total*
Cases	No.	8	126	181	5	320
	Per cent.	2 5	39 5	56·5	1·5	100

Seven of the known ocular pathogens were isolated, alone or in combination (Table III).

Table III *Isolation of bacterial ocular pathogens, in order of frequency*

Pathogen		*Koch-Weeks bacillus*	*Haemolytic streptococcus*	*Pnemococcus*	*Gonococcus*	Staph. pyogenes	*Moraxella*	E. coli	*Total*
Alone		73	54	21	12	6	5	1	172
Combined		12	10	3	4	5	5	1	40
Total	No.	85	64	24	16	11	10	2	212
	Per cent.	40	30	11 3	7·5	5 1	5	0 5	100

The normal ocular flora comprised *C. xerosis* and *Staph. albus*, alone or in combination (Table IV, overleaf). A mixed culture was obtained in 181 cases (Table V, overleaf).

A comparison of Tables IV and V shows that infection with pathogenic organisms affects the growth of the non-pathogenic flora. *C. xerosis* increased in frequency from 12·7 to 32·5 per cent. in the presence of pathogenic bacteria, and *Staph. albus* decreased from 39·7 to 26·5 per cent.

Table IV *Non-pathogenic ocular flora without bacterial pathogens*

Normal flora		C. xerosis *only*	Staph. albus *only*	C. xerosis *plus* Staph. albus	*Total*
Cases	No.	16	50	60	126
	Per cent.	12·7	39 7	47·6	100

Table V *Association of pathogenic and non-pathogenic flora*

Normal	*flora plus pathogens*	C. xerosis	Staph. albus	C. xerosis *plus* Staph. albus	*Total*
Cases	No.	59	48	74	181
	Per cent.	32 5	26·5	41	100

RELATIVE INCIDENCE OF BACTERIA AT DIFFERENT SEASONS (Table VI and Fig. 2)

The Koch-Weeks bacillus is seen to have two peaks, one in Autumn and one in Spring, the former being higher; it is the commonest organism at all seasons, except in Winter when it is replaced by *Strept. haemolyticus*, and it also has a higher incidence in Winter than in Summer.

Table VI *Bacterial pattern of acute conjunctivitis, by season*

Season		*Winter*	*Spring*	*Summer*	*Autumn*	*Total*
Number of cases		40	50	79	151	320
Koch-Weeks bacillus	No.	8	12	13	52	85
	Per cent.	20	24	16 4	34 4	26 5
Haemolytic streptococcus	No.	14	6	7	37	64
	Per cent.	35	12	8·8	24 6	20
Pneumococcus	No.	6	4	7	7	24
	Per cent.	15	8	8 8	4 6	7 5
Gonococcus	No.	2	4	5	5	16
	Per cent.	5	8	6 3	3·3	5
Staph. pyogenes	No.	0	1	5	5	11
	Per cent.	0	2	6 3	3·3	3·4
Moraxella	No.	3	5	1	1	10
	Per cent.	7·5	10	1·2	0 6	3
Staph. albus	No.	22	31	62	112	227
	Per cent.	55	62	78 4	74	70 9
C. xerosis	No.	19	31	55	102	207
	Per cent.	47 5	62	69·6	67 5	64 6
E. coli	No.	0	0	2	0	2
	Per cent.	0	0	2·3	0	0 6

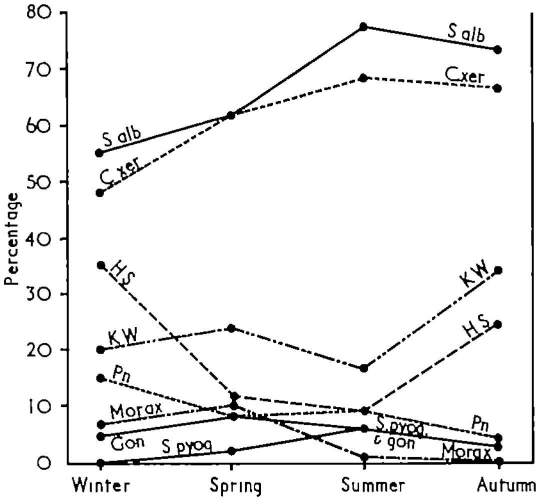

FIG. 2 *Bacterial pattern of acute conjunctivitis at different seasons*

S.alb. = *Staph. albus*
H.S. = Haemolytic streptococcus
K.-W. = Koch-Weeks bacillus
Pn. = Pneumococcus
Morax. = Moraxella
Gon. = Gonococcus
S.pyog. = *Staph. pyogenes*
C.xer. = *Corynebacterium xerosis*

RELATIONSHIP OF ORGANISMS TO AGE AND SEX (Table VII)

We selected the moderate and severe cases of conjunctivitis for our study, but as regards age and sex the selection was random.

Conjunctivitis is seen to be mainly a disease of children, with a maximum incidence at 6 years and under, and it is slightly more common in boys. No cases due to the pneumococcus or gonococcus were reported after the age of 7 years. Twelve of the sixteen cases due to the gonococcus occurred in boys, and nine of the ten cases due to *Moraxella* in girls.

Table VII *Distribution of organisms, by age and sex*.

Organisms	*Age (yrs)*				*Sex*	
	0–1	1–6	6–12	More than 12	Male	Female
Koch-Weeks bacillus	16	34	12	3	44	41
Haemolytic streptococcus	19	32	8	5	36	28
Pneumococcus	18	6	0	0	13	11
Gonococcus	10	6	0	0	12	4
Staph. pyogenes	5	4	1	1	5	6
Moraxella	2	3	3	2	1	9
E. coli	0	2	0	0	2	0
Staph. albus	81	97	26	24	122	106
C. xerosis	82	90	18	17	112	95
Total cases	119	137	35	29	175	145

EFFECT OF DURATION OF DISEASE ON THE ISOLATION OF BACTERIA (Table VIII)

Acute conjunctivitis is a disease of short duration. The majority of cases in this series came to hospital within 8 days of onset. When they were analysed to find the effect of the duration of the disease, it was found that the likelihood of isolating bacterial pathogens diminished slightly with the passage of time.

Table VIII *Rate of obtaining a positive culture, by periods of disease*

Day		1–2	3–4	5–6	7–8	9–10	More than 10
Culture	Pathogens with or without normal flora	54	74	15	26	5	15
	Normal flora only	28	48	13	7	4	16
	Total	82	122	28	43	9	31
Percentage pathogens		65·8	60·6	53·5	60·4	55·5	50

EFFECT OF TREATMENT ON THE ISOLATION OF PATHOGENIC BACTERIA

Many patients had had some sort of treatment either local or systemic before coming to the hospital. Table IX shows that any treatment affected the likelihood of isolating pathogenic bacteria, the organism most affected being the haemolytic streptococcus; but the percentage of positive cultures from cases under treatment is still high, which shows that the treatment was inadequate.

Table IX *Effect of Treatment on Isolation of Pathogens*

Treatment	*Given*		*Not given*	
Organism	*No.*	*Per cent.*	*No.*	*Per cent.*
Koch-Weeks bacillus	29	34·1	56	66·9
Haemolytic streptococcus	18	28	46	72
Pneumococcus	9	37·5	15	62·5
Gonococcus	6	37·5	10	62·5
Staph. pyogenes	4	36·3	7	63·9
Moraxella	4	40	6	60
E. coli	1	50	1	50
Total	71	33·5	141	66·5

ANTIBIOTIC SENSITIVITY (Table X)

The sensitivity of these organisms to a selected group of antibiotics and to sulphadiazine was classified into four categories by the diameter of the zone of inhibition on the plate: *viz.* highly sensitive (H S), moderately sensitive (M S), slightly sensitive (S S), and resistant (R).

Sensitivity was least to penicillin and sulphadiazine, probably because these two drugs tend to be prescribed indiscriminately in hospitals and general practice, often in inadequate doses. Aureomycin (chlortetracyeline) and chloromycetin (chloramphenicol) were found to be the most effective drugs, especially when used topically. Haemolytic streptococci, gonococci, and pneumococci were sensitive to most of the drugs tested.

Table X *Antibiotic sensitivity*

Organism		*Koch-Weeks bacillus*	*Haemolytic streptococcus*	*Gonococcus*	*Pneumococcus*	Staph. pyogenes	*Moraxella*	Staph. albus
Therapeutic agent	Sulphadiazine	R	SS	SS	R	R	R	SS
	Penicillin	R	SS	SS	SS	R	R	R
	Streptomycin	R	HS	HS	HS	MS	R	MS
	Chloramphenicol	HS	HS	HS	HS	HS	HS	HS
	Tetracycline	SS	HS	HS	HS	SS	SS	MS
	Chlortetracycline	HS	HS	HS	HS	SS	MS	MS
	Oxytetracycline	MS	HS	HS	HS	SS	SS	HS

Discussion

Conjunctivitis is known to occur in seasonal epidemics, generally in the Spring and Autumn. This seasonal variation is related to the fly population which is the vector for transmission of the disease, a fact which was observed nearly a century ago by Howe (1888) and has since been amply confirmed by Lyons and Abdine (1952) and Ponghis (1957).

In 131 cases of this series (about 40 per cent.), a negative culture was obtained or one or more of the normal ocular flora was grown. This absence of known pathogenic bacteria raises several questions. The inhibitory effect of lysozyme and the misdiagnosis of early cases of trachoma as acute bacterial conjunctivitis should be borne in mind. Adenoviruses, which fail to grow on ordinary bacteriological media, have been shown to cause conjunctivitis (Bell, Snyder, and Murray, 1960; Kasel, Evans, Spickard and Knight, 1963), as well as pleuropneumonia-like organisms (PPLO) (Warthin, 1948; Krücken and Fabry, 1955; Holland and Worlton, 1957; Weinberger, Ropes, Kulka, and Bauer, 1962). The possibility that organisms failed to grow because some of the patients had already received treatment should also not be overlooked.

The question must also be raised whether the so-called nonpathogenic flora, such as *C. xerosis* and *Staph. albus*, are in fact potential pathogens. Some maintain that the only criterion of pathogenicity should be that an organism is found to be parasitic on living cells (Lindner, 1921; Pillat, 1921). This view would rule out organisms like *Staph. albus* from any active part in conjunctival pathology, yet this organism was found in 110 genuine cases of acute conjunctivitis either alone or associated with *C. xerosis*. The role of this organism as a potential pathogen in acute conjunctivitis therefore needs to be further studied, and such work is now in progress.

C. xerosis was isolated in 209 of our 320 cases, and in sixteen cases was the only organism found. It is known to be an almost constant inhabitant of the conjunctival sac, but the earliest attempts to incriminate it as a pathogen were fruitless both clinically (Weeks, 1887) and experimentally (Fraenkel and Franke, 1887). This organism could hardly exist alone in the conjunctiva, and it probably depends for its existence on other organisms in symbiosis.

The data presented in Tables IV and V show that, in cases of conjunctival inflammation, the local flora change considerably (Duke-Elder, 1965), since isolations of *C. xerosis* more than doubled and those of *Staph. albus* decreased.

The isolation of *Staph. albus* in 232 cases (72·5 per cent.) confirms the findings of other workers that this organism is more prevalent in the conjunctivae in hot climates (62 per cent. in Queensland, Gibson, 1951; 95 per cent. in Egypt, Kamel, 1949), and less prevalent in cold climates (*e.g.* Great Britain: 34 per cent. in healthy conjunctivae (Smith, 1954), 11·3 per cent. in cases of conjunctivitis (Jones, Andrews, Henderson, and Schofield, 1957)).

The Koch-Weeks bacillus was the commonest pathogenic organism isolated in this series at all seasons except the Winter. The autumn peak is higher and is followed by a post-autumnal peak which means that it is isolated more often in Winter than in Summer. This is a feature of Assiout epidemics in contrast to other parts of Egypt, and may be due to the fact that autumnal weather extends for a longer period at Assiout. In cool countries such as Great Britain, the Koch-Weeks bacillus is rarely encountered in conjunctivitis (Duke-Elder, 1965) and its peak is known to occur in late Winter (Jones and others, 1957). In North Africa and the Middle East there are peaks in May and September (Wilson, 1935; Huet, 1956; Ahmad, 1958).

The haemolytic streptococcus was the next most frequent organism, although streptococci are rarely found in the conjunctival sac, being present in only 1 to 4 per cent. of normal eyes (Duke-Elder, 1965). This and the pneumococcus were more commonly encountered in the Winter season, which may be related to the Winter prevalence of upper respiratory tract infection.

The gonococcus is known to be a common cause of acute conjunctivitis in Egypt (Wilson, 1935; Lyons and Amies, 1949), but was fourth in frequency in our series. Whether this is due to a low incidence of venereal diseases in Upper Egypt is open to further investigation.

The pneumococcus was isolated in only 24 cases (7·5 per cent.); it is found in healthy conjunctivae in varying proportions: 3·2 per cent. (Smith, 1954) and 10 to 12 per cent. (Lundsgaard, 1927). It is difficult to determine how far it should be regarded as a pathogen but it was found alone in 21 of the 24 cases in which it was isolated.

Moraxella was found in ten cases (about 3 per cent.), and in half of these it existed with other pathogens. This organism, which is known to produce subacute angular blepharoconjunctivitis rather than acute diffuse inflammation, was found by Smith (1954) in a small proportion of healthy conjunctivae, but has also been reported in 1 per cent. of cases of acute conjunctivitis (Jones and others, 1957). There are at least four different strains of *Moraxella* (Murray and Truant, 1954) to which the conjunctiva may react differently.

E. coli was isolated in only two cases; in one of them it was found in pure culture. It has been isolated from the conjunctival sac in 2 per cent. of normal individuals (Smith, 1954), but Sadoughi (1948) thought that it was usually a contaminant. It was obtained in pure culture in acute conjunctivitis by Sanyal (1929) and Friedenwald (1929). Infection in guinea-pigs has been shown to produce purulent keratoconjunctivitis (Rédey and Csizmazia, 1960).

Summary

(1) 320 cases of acute conjunctivitis seen at the Assiout University Eye Clinic were investigated bacteriologically and epidemiologically.

(2) In 189 cases (59 per cent.), one or more of the known bacterial ocular pathogens was isolated, either alone or associated with normal flora.

(3) In 131 cases (41 per cent.), normal flora or a negative culture were obtained.

(4) The commonest pathogen was the Koch-Weeks bacillus, followed by haemolytic streptococcus, pneumococcus, and gonococcus. Two cases were possibly due to *E. coli.*

(5) A marked increase in the frequency of isolation of *C. xerosis* was found in cases infected with pathogens.

(6) Koch-Weeks bacillus was the most common cause of conjunctivitis at all seasons (except the Winter where it was replaced by the haemolytic streptococcus) and occurred in epidemic peaks in the Spring and Autumn.

(7) Conjunctivitis was found most often in the first 6 years of life. The gonococcus was more commonly isolated from males and *Moraxella* from females.

(8) The isolation of pathogenic bacteria from the conjunctiva was affected by the duration of the disease and by previous treatment of any sort.

(9) The pathogens isolated in this series were found to be totally or highly resistant to penicillin and sulphonamides and markedly sensitive to chlortetracycline and chloramphenicol.

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Applanation tension and axial length of the eyeball

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Armaly (1967a) found, from two independent studies of first-degree relatives with clinically normal eyes, that the level of ocular tension is genetically determined and that the mode of inheritance is polygenic multifactorial in nature. In a previous study (Armaly, 1966), he showed that the applanation tension in one partner of a marital pair is independent of the other's, which led to the conclusion that environmental influence is small.

The effects of age and sex on ocular tension have also been evaluated (Armaly, 1962), and from an extensive population survey it was concluded that a significant difference in tension exists between different age groups, both Schiötz and applanation readings becoming higher and C values becoming lower with advancing age. In a later paper, however, Armaly (1967b) found that the effect of age and sex was limited to the age groups over 45 years; women in these groups have significantly higher means of applanation and Schiötz readings than men.

The present survey concerns:

(*a*) The relationship of axial length of the eyeball to its tension;

(*b*) The differences in ocular tension between myopes, hypermetropes, and emmetropes;

(*c*) The effect of the sex of subjects within the same age group on applanation tension.

Subjects

For the part of this survey concerned with (*a*) and (*c*) above, the same individuals who had been studied for the determination of the relationship between the cup-to-disc ratio and the length of the eyeball (Tomlinson and Phillips, 1969) were used, *i.e.* 75 undergraduate students. Their ages were between 18 and 27 years; 26 were female and 49 male. The result from only one eye of each subject was used for statistical purposes: it was randomly selected by the toss of a coin (36 right, 39 left).

For the study of (*b*) above, to this original sample were added the results from a group of nineteen normal persons whose ages varied between 26 and 72 years, making a grand total of 94 subjects. Of the nineteen additional subjects, twelve were female and seven male, and thirteen left eyes and six right eyes were included. The reason for adding to the original sample of 75 was that the difference in applanation tension between the refractive groups did not quite reach the 5 per cent. level of significance (although the correlation between applanation tension and axial length did); wider ranges of refractive errors therefore became available, from a range of −7 D to +4·75 D in the sample of 75 to a range of −9·5 D to +9·5 D in the sample of 94.

Method

The ocular tensions of all subjects were obtained with the applanation tonometer mounted on the Haag-Streit 900 slit lamp. Also available for all subjects were the following measurements:

(*i*) Depth of the anterior chamber (measured optically with the attachment for the slit lamp);

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(*ii*) Distance from the anterior corneal surface to the anterior retinal surface, obtained from a combination of optical and ultrasonographic measurements (technique similar to that of Leary, Sorsby, Richards, and Chaston, 1963);

(*iii*) Refraction of the eye measured objectively and subjectively.

Results

(A) AXIAL LENGTH AND APPLANATION TENSION

The relationship between these two was statistically analysed for the 75 subjects in the age group 18 to 27 years, with the rank correlation method of Spearman. A correlation coefficient of +0·367 which was significant at the 0·2 per cent. level by Student's "t" test was found, *i.e.* the greater the axial length the higher the ocular tension. A scattergram is shown in the Figure together with the regression line for values of applanation tension on values of axial length. A correlation coefficient of +0·34, significant at the 0·1 per cent. level, was also found from a rank correlation test on the enlarged group of 94 subjects.

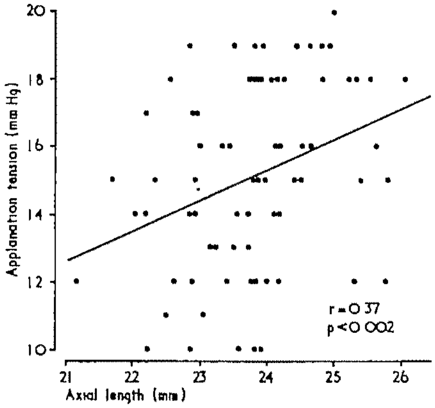

FIGURE *Regression line shown on scattergram obtained from data on a group of* 75 *normal subjects aged* 18 *to* 27 *years* (*myopes* 32, *emmetropes* 27, *and hypermetropes* 16). *Correlation significant at* 0·2 *per cent. level*

(B) REFRACTION AND APPLANATION TENSIONS

The sample of 94 was subdivided into:

(*a*) 37 myopes: best sphere refraction more ametropic than −0·5 D.
(*b*) 22 hypermetropes: best sphere refraction more ametropic than +0·5 D.
(*c*) 35 emmetropes: best sphere refraction not more ametropic than ±0·5 D.

The mean and standard deviation of applanation tensions were found in each group (Table I). A significant difference (t = 2·41; P < 0·02) was found between the means

Table I

Refractive group	*Applanation tension (mean ± S.D.) (mm. Hg)*	*Axial length (mean ± S.D.) (mm.)*
Myopia	15·49 ± 2·81*	24·61 ± 1·00*
Emmetropia	14·74 ± 2·42	23·40 ± 1·38
Hypermetropia	13·91 ± 2·28*	22·53 ± 1·02*

* Significant difference between means at 2 per cent. level

of applanation tensions in the myopic and hypermetropic groups, the former being the greater. This result is consistent with the observation in the previous Section A above. The difference between the emmetropes on the one hand and each of the two groups of ametropes on the other was not significant (myopes *v.* emmetropes $t = 1{\cdot}17$, $P < 0{\cdot}25$; hypermetropes *v.* emmetropes $t = 1{\cdot}46$, $P < 0{\cdot}25$), but their mean level of tension fell nicely between the two which indicates some internal consistency.

Of the astigmats in the survey, 65 had less than 1D, eight had >1D but <2D, and two had >3D. The range of best sphere refraction for the 18 to 27 year age group was −7D to +4·75D, while that for the 18 to 72 year age group was −9·5D to +9·5D.

(C) SEX AND APPLANATION TENSIONS

The mean and standard deviation of applanation tension and axial length were found for the male and female samples within the age range 18 to 27 years. The males had significantly higher applanation tensions and axial lengths than the females within this age group (Table II, top half).

Table II

Sample	*Applanation tension (mean ± S.D.) (mm. Hg)*	*Axial length (mean ± S.D.) (mm.)*
Males	15·58 ± 2·83*	23·98 ± 1·00*
Females	14·25 ± 2·75*	23·50 ± 0 76*
Males, chosen with axial lengths to match closely those of females	15·08 ± 2·78†	23·56 ± 1·08†
Females	14 25 ± 2·75†	23·50 ± 0 76†

* Significant difference between means at 5 per cent. level
† Difference between means not significant

In order to assess this sex difference more stringently, a group of males was chosen so that each individual's axial length was matched as closely as possible with that of a female; comparison between applanation tensions of this male "control" group and the female group showed no significant difference (as also, of course, between their axial lengths).

Hypothesis

The explanation for these findings is not obvious but a common basis is more attractive than two independent ones. One possible explanation is that, at the time when myopia develops, there is a level of production of aqueous humour too great for slightly subnormal outflow channels so that the eyeball distends. As a result, the corneal circumference and the antero-posterior extent of the meshwork probably increase so that a greater cross-sectional area of outflow channels is available; thinning of the ciliary body and the sclera may also increase uveo-scleral bulk flow (see Bill, 1965): neither of these changes is enough to compensate fully for the higher level of production of aqueous humour, hence the raised pressure in myopic eyes. The opposite explanation may well be true, however: that as a result of the inherited greater axial length of the myopic eyeball, the resistance to outflow of aqueous humour is increased (perhaps mainly by flattening and attenuation of the meshwork); to put this more generally, axial length will be one of the quite important inherited factors in the multifactorial polygenic inheritance of open-angle glaucoma (see Armaly, 1967a).

An attractive feature of either explanation, possibly favouring the first-mentioned, is that compensatory corneal flattening would be easily understood as a coincidental consequence which would contribute to the achievement of emmetropia, and the increase in corneal diameter might be a determining factor in the relatively thinner crystalline lens; perhaps the hypothesis should be restricted only to cases of low myopia, or of emmetropia with a greater than usual axial length, and not applied to high myopia, for which a different (genetic) explanation may exist (Luyckx-Bacus and Weekers, 1967).

Finally, our observations may have another common basis not immediately obvious.

Discussion

Further evidence for or against that inference would be obtained by a study of tonometry in cohorts of myopes and normals, especially at the age when myopia is starting or quickly progressing. Treatment of developing myopia with drugs to reduce ocular tension would have a rationale—but such treatment, by preventing an increase in axial length, could possibly prevent an increase in outflow of aqueous through conventional channels or through uveo-scleral channels, so that the danger of glaucoma might eventually be increased.

Might the results of this survey be due merely to a tonometric artefact resulting from the tendency for myopic eyes to have flatter corneal curvatures than emmetropic and hypermetropic eyes (Sorsby, Benjamin, Davey, Sheridan, and Tanner, 1957)? This was considered in the light of the work of Schmidt (1956), who has shown that applanation tensions observed in the case of *very* flat corneal curvatures are greater than those recorded in the case of *very* steep corneae. Corneal curvature in our survey ranged from 7·08 to 8·55 mm. radius. Over this range of curvature for normal ocular rigidity, Schmidt observed a change of only 0·1 mm. Hg in applanation tonometry, and we feel therefore justified in accepting for our survey the conclusion of Goldmann (1956) that for "normal limits" the effect of corneal curvature on applanation tension is negligible.

Tonometry artificially raises the intraocular pressure. In an eye with a large volume and low rigidity the rise would be expected to be less than in a small eye. This would tend to discriminate *against* our finding of high pressure in the eyes with the greater axial length and to neutralize any effect of corneal curvature alone.

Although Armaly (1967b) found no significant sex difference in applanation tensions below the age of 45 years, in our subjects the difference was significant at the 5 per cent. level (see Table II). Possibly there is less inconsistency than might appear because our subjects had a fairly large range of ametropia, and therefore of axial length. Furthermore, as we have mentioned in "Results" above, if a series of males and females, carefully matched for axial length, is examined, no significant difference in pressure is found; these subjects were in the age range 18 to 27 years, but it would be interesting to know if a positive correlation between tension and axial length exists in all age groups.

The observations recorded here are consistent with the high incidence of myopia in patients suffering from simple glaucoma; Perkins and Jay (1960) reported that 22 per cent. of 205 patients with the condition over the age of 50 were myopic; under the age of 50 the incidence of myopia was 37·8 per cent. The high incidence of simple glaucoma in myopic patients has been observed by Weekers, Lavergne, and Prijot (1958) and by Diaz-Dominguez (1961, 1966), who found this incidence in eyes with more than −20 D of myopia and suggested that malignant myopia may be a specific form of congenital glaucoma. Our results are also consistent with those of Armaly and Sayegh (1969) and

Armaly (1969), who found, for example, that the cup-to-disc diameter ratio tended to be more frequently >0·3 the higher the ocular tension, even though (or perhaps because?) their sample excluded any subject with a distance refraction of greater than 3D myopia or with a history or evidence of ocular disease, injury, or operation; in the older age groups the frequency of large cup-to-disc ratios was greater. Armaly and Sayegh found a negative correlation of cup-to-disc ratio with facility of outflow and have made the suggestion that these genetically determined parameters (applanation tension and facility of outflow) share common determinants. Our observations suggest that a basic common factor is axial length. This concept may be regarded from a more general point of view. Armaly (1965), considering the distribution of applanation pressure in the general population, suggested that this population was made up of statistically different sub-populations, in which age, sex, and family history of glaucoma are three of the determining factors. Our observations seem to justify the suggestion that axial length of the eyeball, which implies in many cases spherical ametropia, should be included among the factors mentioned.

It is at first sight a little surprising that, unlike Armaly and Sayegh (1969), we have found no significant correlation between cup-to-disc ratio and applanation tensions, although we have found that each separately showed a significant correlation with axial length (Tomlinson and Phillips, 1969). However, their sample was much larger than ours and we do not consider that there is any true inconsistency between our results. Some support for that may be claimed because Armaly (1969) found the correlation between applanation tensions and cup-to-disc ratio less powerful than that between C values and cup-to-disc ratios. (We did not include C values in our study.) We suggest that axial length, which we have shown to be correlated with cup-to-disc ratio (Tomlinson and Phillips, 1969), also affects C values *via* "ocular rigidity", in which total ocular volume or surface area of corneo-scleral envelope (see Phillips and Quick, 1960; Ytteborg, 1960; and Phillips and Shaw, 1970) is probably an important element. A residual effect may be present even if a correction factor for ocular rigidity be included (see Gloster, 1966).

Summary

A group of 37 myopes aged 18 to 72 years showed a mean applanation tension of 15·49 mm. Hg (S.D. 2·81) which was significantly higher than the mean of 13·91 mm. Hg (S.D. 2·28) in a group of 22 hypermetropes. The mean of 35 emmetropes was 14·74 mm. Hg (S.D. 2·42), *i.e.* nicely between the other two groups; this mean did not differ significantly from the other two.

There was a statistically significant positive correlation between ocular tension and axial length, *i.e.* the higher the tension the greater the axial length. The group used for this study comprised 75 persons aged 18 to 27 years of the total of 94 mentioned in the preceding paragraph.

Although males had a significantly higher tension than females, they also had significantly larger axial lengths; when a series of male : female pairs was chosen so that each pair had as nearly the same axial length as possible, the differences between the means of the tensions became very small (insignificant), *i.e.* if the groups were controlled for axial length the sex difference in tension almost disappeared.

These findings are consistent with the recorded statistics which suggest that myopia is more common among patients with open-angle glaucoma than among normal individuals.

Two possible explanations are immediately obvious: EITHER raised tension is an important factor in producing a large axial length OR the raised tension is produced by a large axial length. However, other common bases for our observations may exist.

Addendum

Since this paper was written, observations have been published (Abdalla and Hamdi, 1970) showing that in all age groups from 11 to over 50 years, except for 21 to 30 years, myopes had significantly higher ocular tensions than emmetropes.

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Relationship between serum osmolality and intraocular pressure in normal and diseased eyes

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Patterns of diurnal change in blood osmolality and in intraocular pressure are recognized (Duke-Elder, 1958). Davson (1969) has pointed out that, although the difference in osmolality between the aqueous humour and the eye contributes to the intraocular pressure, considerable changes in osmolality and flow into the eye will be accompanied by relatively small changes in intraocular pressure. Moreover, previous studies (Hempel, 1964; Iverson and Brown, 1967) have demonstrated no direct relation between physiological serum osmolar variation and intraocular pressure. Hempel suggested that intraocular pressure and serum osmolar variations were due to an underlying adrenocortical rhythm, a "biological time clock". It is, however, well established that osmotically active agents alter intraocular pressure when given for experimental, diagnostic, or therapeutic purposes (Davson and Thomassen, 1950; Galin, Aizawa, and McLean, 1959, 1961a). These are acute changes and are associated with unphysiological fluctuations in serum osmolality (Galin and others, 1961a). *A priori* it would seem that any osmotic change would have some effect on intraocular pressure unless masked by homeostatic mechanisms or by pathological variations in aqueous production or outflow in the eye. Galin and others (1961b) have called the glaucomatous eye a "sensitive osmometer", but previous studies suggest that it is too insensitive to reflect the slow and slight changes of the diurnal pattern.

The present study is another investigation into the relationship between normal diurnal osmolality changes and intraocular pressure.

Material and methods

A population consisting of persons with glaucoma or "ocular hypertension" or "normal" eyes was studied. In all the seven glaucoma cases the discs were cupped and the intraocular pressures quite abnormal and the fields showed glaucomatous loss or at least contraction (see Table I). The glaucoma cases were all taken off treatment well before the study or had never been on treatment. Four of the five cases of ocular hypertension had normal discs and normal fields but the fifth patient was found to have early glaucoma field loss when examined about 2 years after the osmolality study (see Table I). The seven "normal" cases had normal discs and low normal pressures. Field examinations were not performed in the normal group.

Applanation tonometry with withdrawal of a venous blood sample shortly after tonometry was done at a roughly equal (usually 2-hourly) intervals from about 9.30 a.m. to 3.30 p.m. in each case. No restriction was placed on diet or activity and a number of the persons were out-patients. Applanation tonometry and osmolar determinations using a Fiske osmometer were performed as part of the daily routine by technicians who were unaware of the nature of the study.

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Table I *Findings in nineteen subjects*

Group	*Case no.*	*Age (yrs)*	*Diagnostic features*	
Glaucoma	1	36	Glaucoma discs Pathological pressures	Field complicated by retinitis pigmentosa
	2	66		Glaucomatous field loss
	3	61		
	4	71		
	5	59		
	6	63		
	7	63		
Ocular hypertension	8	51	Normal discs Raised pressure	No glaucomatous field change
	9	54		Late field change
	10	63		Normal fields
	11	46		
	12*	62		
Normal	13	56	Normal fundi Low normal intraocular pressure	
	14	68		
	15	56		
	16	68		
	17	64		
	18	64		
	19	49		

*Unreliable witness

A regression analysis was then performed on the data. It was implicit that the intraocular pressure points were not necessarily assumed to have a normal distribution. To facilitate the analysis pressure readings in right and left eyes for each osmolality value were averaged and the analysis was performed on these mean values.

Results (Table II)

There were no significant differences between the slopes of the regressions of pressure on osmolality either between individuals, between different groups, or between sets of readings between individuals within groups.

Table II *Results*

Regression analysis	*Regression coefficient*		*Significance*
Between groups	0·390		Not significant
Between individuals within groups	0·205		Not significant
Between readings within individuals	(*a*) Glaucoma	—0·328	Significant at 5 per cent. level
	(*b*) Ocular hypertension	—0·512	Significant at 1 per cent. level
	(*c*) Normal	—0·043	Not significant

On the other hand, within diseased eyes or within "hypertensive" eyes there is a statistically significant inverse relationship between intraocular pressure and osmolality and this relationship is especially evident within the hypertensive eyes.

There were highly significant ($P < 0.1$ per cent.) differences between individuals within groups with regard to their osmolality. Mean group osmolality values were: Normal, 291; Glaucoma, 293; Hypertension, 298.

The osmolality value for the hypertension group is highly significantly different ($P < 0.1$ per cent.) from the values for the other two groups which are not significantly different from one another.

Discussion

These data confirm the absence of any significant overall relationship between osmolality and pressure already noted by Hempel (1964) and Iverson and Brown (1967). Further analysis, however, shows that within abnormal eyes there is a general tendency for there to be a negative relation between osmolality and intraocular pressure but the pressure "response" to osmolar fluctuations is individual and one cannot predict that a high or low osmolality reading in different individuals will reflect any particular difference in their intraocular pressures either within or between groups. Osmolar values vary significantly between and within groups and it is tempting to think that the higher osmolar values in the hypertension group are reflected in the closer relationship between osmolality and pressure within the individuals of this group. The author is, however, quite uncertain why the mean osmolality is different in this group. Teleologically it seems most unlikely to be a response to pressure elevation in the eye.

The absence of any apparent relationship between serum osmolality and intraocular pressure in "normal" eyes is to be expected as the outflow facility and secretion rate will vary to produce the desired homeostatis should there be a serum osmolar change.

Summary

The relationship between serum osmolality and intraocular pressure was investigated in persons with "normal" eyes and in subjects with chronic glaucoma and in subjects with "ocular hypertension". Regression analysis of the data showed that there was no relationship present in normal eyes but that in both ocular hypertension and glaucoma individuals showed a significant inverse relationship between osmolality and pressure, although the response was idiosyncratic and there was no overall group or between-group relationship between the parameters.

The author gratefully acknowledges the help received from Dr. Antonovics of Stirling University who most kindly undertook a large part of the statistical analysis of the data. He wishes to thank Dr. C. R. S. Jackson and Dr. J. Hughes for the facility of making this study on patients under their care.

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Pigment dispersion in a case of Alport's syndrome

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The syndrome of hereditary nephritis and perceptive deafness was first recognized by Alport (1927), although reports suggestive of this association date from the latter part of the 18th century. The syndrome has since been widened to include certain ocular defects, such as lenticonus, microspherophakia, and lens opacities, and about 100 families have been described in the world literature. In recent years there have been several detailed reviews of the syndrome (Perkoff, Nugent, Dolowitz, Stephens, Carnes, and Tyler, 1958; Shaw and Glover, 1961; Crawfurd and Toghill, 1968), including one of the ophthalmological findings (Arnott, Crawfurd, and Toghill, 1966). This present report concerns a new family with previously unrecorded ocular defects.

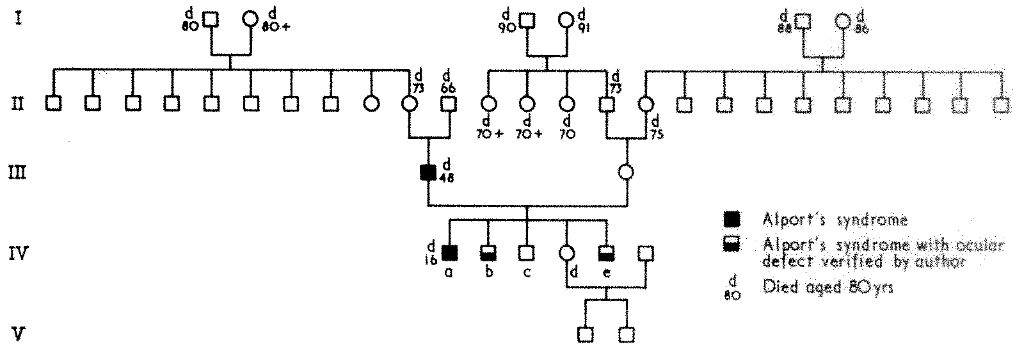

FIG. 1 *Pedigree of family with Alport's syndrome*

Case reports

The last five generations of this family, shown in Fig. 1, include affected kindred in Generations III and IV. The two individuals who have been studied in most detail are IVb and IVe, but all surviving descendants of IIIa have been examined and the syndrome excluded.

IVb. This young man aged 25 years was first seen at the renal clinic, to which he had been referred from a provincial hospital for assessment of chronic renal failure and suitability for long-term renal dialysis. His perceptive deafness was first noted at this time and, in addition, the presence of what were thought to be lens opacities completed the diagnostic triad of renal, auditory, and ocular defects that comprises Alport's syndrome. He was subsequently examined in the Eye Department,

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where it was noted that he considered his visual acuity to be normal but that he had been troubled by photophobia for over 10 years. Examination revealed the following:

Visual acuity Right 6/18 partly; left 6/24 (corrected).

Pupils These were unusually large at 4·5 mm. diameter in bright summer daylight, but reacted briskly to stimuli although the magnitude of the response was poor. It was found that mydriatics (gutt. homatropine and cocaine, cyclopentolate hydrochloride 1 per cent., phenylephrine hydrochloride 10 per cent.) produced a rapid and profound mydriasis so that the lens zonule could be easily seen with a loupe. The irides were markedly atrophic and this was thought to be the explanation of the above findings.

Corneae A fine dusting of pigment granules was present on the posterior corneal surface; this was more dense inferiorly and, in addition to this general pigment dusting of the endothelium, well-defined Krukenberg spindles were present in both eyes. Gonioscopy revealed both angles to be wide open but with a large quantity of pigment on the trabecular meshwork. The ocular tensions were normal (right 15 mm. Hg, left 16 mm. Hg). Provocative tests for glaucoma (water-drinking, dark-room, and mydriatic tests) gave negative results.

Lens A well-marked bilateral anterior lenticonus was present and, on the roughened anterior lens capsule that corresponded with the lenticonus, there were considerable pigment deposits (Fig. 2); these were also present in the intersections of the zonular attachments to the lens capsule.

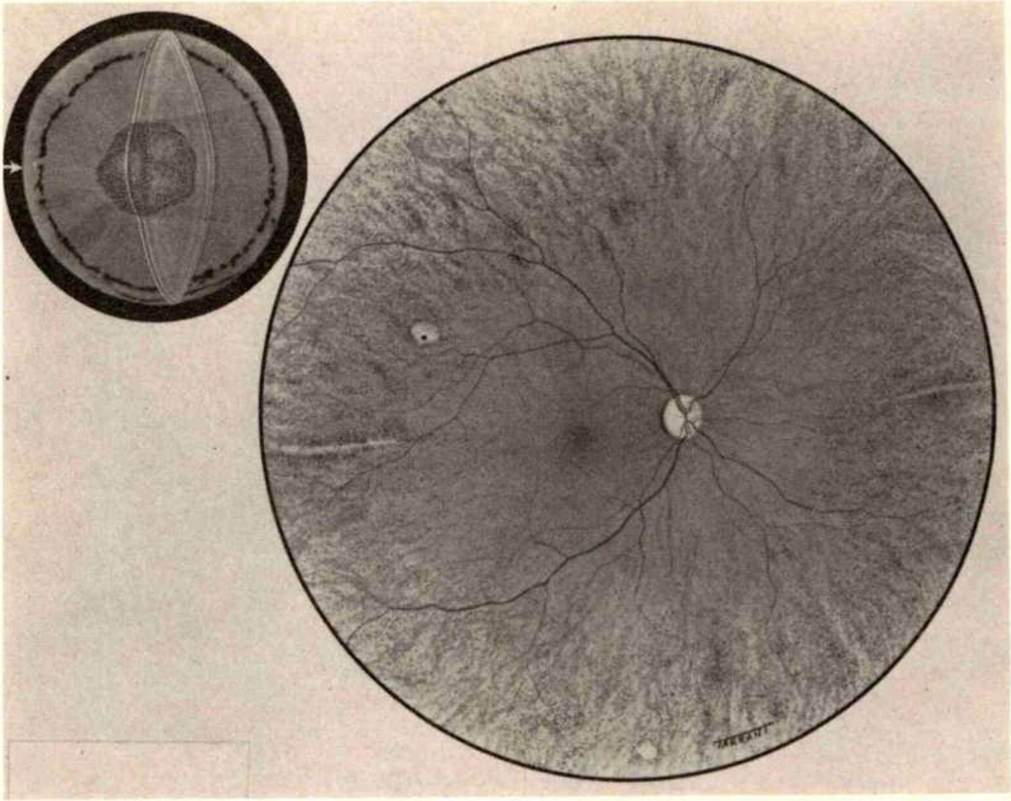
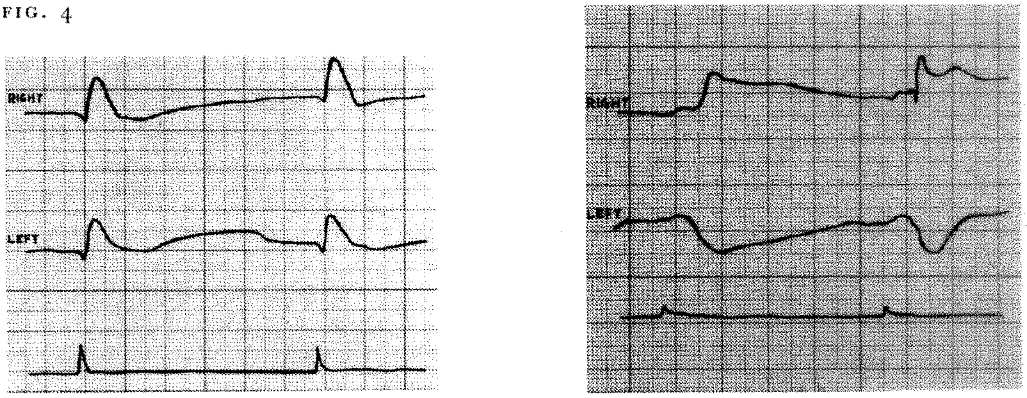


FIG. 2 *Patient IVb. Painting of lens, showing pigment deposits on anterior lenticonus and among attachments of zonule to posterior lens capsule*

FIG. 3 *Patient IVb. Painting of fundus, showing numerous small pigment deposits at periphery of retina*

Fundi The retina of each eye was thinned peripherally with numerous small aggregations of pigment extending posteriorly behind the equator (Fig. 3). The visual fields and colour discrimination were normal, as were the electroretinogram (ERG) and the electro-oculogram (EOG) at the first examination in June, 1968. Re-examination some 15 months later in October, 1969, showed that the fundus changes described above extended further posteriorly and that the visual acuity had deteriorated to right 6/36 and left 6/60 (corrected). The visual fields, colour discrimination, and EOG remained normal but the ERG was abnormal with an absent "b" wave, typical of tapeto-retinal degeneration (Fig. 4). In view of the discrepancy between the ERG and the visual fields, the former was repeated in late November, 1969, and on this occasion the "b" waves, although quantitatively in the lower range of normal, were qualitatively normal. In view of the equivocal results obtained with the ERGs, this patient cannot at this stage be regarded as having a tapeto-retinal degeneration.

FIG. 4



July 5, 1968. *Scotopic ERG at* 13 *min.*
Calibration 20 *mm.* = 500 μ*v*
a-wave 37·5 μ*v normal, b-wave* 225 μ*v*

EOG, Right 192 *per cent., Left* 180 *per cent.*

October 2, 1969. *Scotopic ERG at* 10 *min.*
Calibration 20 *mm.* = 500 μ*v*
a-wave minimal, b-wave subnormal

EOG, Right 150 *per cent., Left* 170 *per cent.*

IVe. A boy aged 15 years was first seen during the general survey of this family. His general health was described as excellent and he had no symptoms referable to his eyes. Examination revealed:

Visual acuity Right 6/9; left 6/7·5 (corrected).

Pupils Normal in size and response.

Media and fundi Both lenses showed a mild anterior lenticonus, but there was no evidence of pigment dispersion as in his elder brother (IVb). Fundus examination showed minimal peripheral retinal thinning only.

General examination A mild perceptive deafness was noted and confirmed by audiometry. Urine analysis revealed an albumin content of 1 g./l., but no casts were seen. Blood chemistry and clearance studies were normal.

IIIa and IVa. Both these kindred, the father and elder brother respectively of the two affected males described above, died of malignant hypertension and its sequelae. Both were known within the family to be deaf and, although they are not recorded as having any ocular abnormality, there is little doubt that they also suffered from Alport's syndrome.

Discussion

(1) OCULAR DEFECT

The pigment granules found to be present on the posterior corneal surfaces, anterior iris surfaces, and on both anterior and posterior lenticular surfaces, together with the dense trabecular pigment of patient IVb, appear to have resulted from the liberation of pigment from the atrophied iris pigment epithelium, and indeed pigment granules were seen floating free in the aqueous on several occasions. Sugar (1967), discussing pigmentary glaucoma, recognized this group of findings as constituting a "pigment dispersion syndrome" and considered pigmentary glaucoma to be a late feature of the syndrome. Certainly patient IVb shows no evidence of glaucoma at the present time, but now that his life-expectancy has been prolonged by renal transplant it will be interesting to see whether he develops glaucoma in future years.

The previously reported ocular lesions of Alport's syndrome have affected the lens or its capsule and consequently the significance of the fundus appearances described above remains in doubt, particularly in view of the equivocal ERG results, and whether a typical tapeto-retinal degeneration develops in the future remains to be seen.

Crawfurd and Toghill (1968) discussed the possible reasons for the relatively small number of cases, approximately 15 per cent., of Alport's syndrome in which ocular involvement has been noted. Although failure to recognize ocular lesions, particularly the less marked changes, cannot alone explain this deficiency, it seems probable that a number could be accounted for in this way. In support of this contention, it may be noted that the young male IVe was asymptomatic and that the ocular lesion (anterior lenticonus) was diagnosed only after slit-lamp examination, the ophthalmoscopic appearances being normal. Secondly, even his severely affected brother IVb considered his visual acuity to be normal at 6/24 in each eye, presumably because he had grown up to accept such vision as normal. Consequently, if Alport's syndrome is not suspected from the family history, it is unlikely that the milder ocular abnormalities will be detected on routine medical examination and even patients with well-marked lesions cannot be relied upon to volunteer symptoms referable to the eyes.

(2) GENETIC DEFECT

The limited number of generations with affected individuals in this family precludes any fresh conclusions being drawn as to the mode of inheritance of the disease. It is probable that the initial mutation occurred in patient IIIa, since the members of the previous generations, maternal and paternal, all either died in old age of apparently unrelated causes or are still alive. Crawfurd and Toghill (1968) brought the pedigree of Alport's original family up to date, and noted that the condition tended to die out after a few generations. However, now that renal dialysis and transplantation offer even the most severely affected individuals a reasonable life-span and the possibility of raising a family, this tendency may be reversed.

Summary

The clinical features of a "pigment dispersion syndrome" with possible retinal degeneration in addition to the usual features of the disease are described in a member of a previously unreported family with Alport's syndrome.

I should like to thank Mr. J. R. Hudson and Dr. S. Cameron for permission to publish this report on patients under their care: and for helpful advice.

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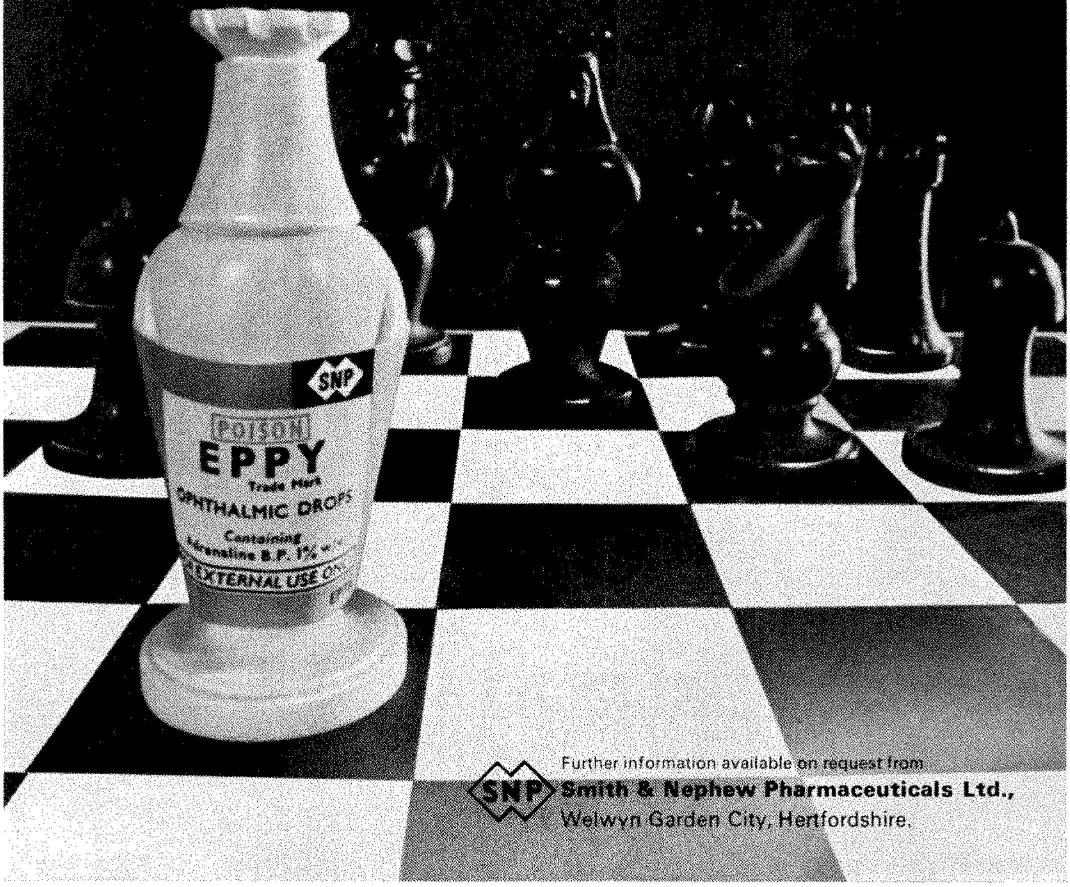

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Brit. J. Ophthal. (1970) **54**, 562

Solitary xanthoma of the limbus

MERRILL GRAYSON AND DAN PIERONI

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The purpose of this report is to present the findings in a case of solitary xanthoma of the limbus. Previous reports of ocular xanthomata have been associated with some other clinical or metabolic dysfunction, but in the case presented no other associated abnormalities could be found.

Case report

An 11-year-old Caucasian boy was seen at the Indiana University Medical Center, Department of Ophthalmology, because of a yellow limbal lesion of the left eye which had been first noted 2 years previously, and which had been progressively enlarging. The family history was not contributory. The child was premature, but developed normally with no history of significant systemic or ocular disease. There was no history of ocular trauma. The general physical examination was within normal limits. Specifically, no dermatological sign of xanthoma formation was found and hepato-splenomegaly was not present. The visual acuity was 20/20 in the right eye and 20/70 in the left.

The yellowish, raised mass measured 6 × 7 mm. in diameter at the medial limbus and encroached upon the pupillary area (Fig. 1). Several large trunk vessels penetrated the mass. Thin needle-like, multicoloured crystals were noted in the mid-stroma of the cornea bordering the advancing edge of the lesion.

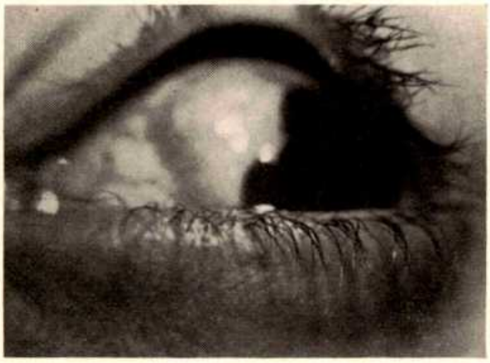

FIG. 1 *Yellow raised limbal xanthoma*

Removal of the tumour was performed, and a conjunctival flap was pulled over the area of excision and sutured into place. There were no postoperative complications, and the patient showed no evidence of recurrence when seen 7 years postoperatively.

Laboratory investigations Urine analysis normal; cholesterol 172 mg. per cent. (normal 50 to 250); cholesterol esters 124 mg. per cent. (normal 100 to 150); neutral fat (triglycerides) 79 mg. per cent. (normal 150 to 180); blood urea nitrogen 18 mg. per cent.; uric acid (blood) 5·2 mg. per cent.; electrolytes normal.

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Address for reprints: Merrill Grayson, M.D., 1100 West Michigan Street, Indianapolis, Indiana, 46202, U.S.A.
*Supported in part by a grant from Research to Prevent Blindness, Inc., New York
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X rays of skull, chest, long bones, and pelvis normal.

Follow-up serum lipid studies, performed 7 years postoperatively, revealed: cholesterol 167 mg. per cent.; cholesterol esters 136 mg. per cent.; triglycerides 69 mg. per cent.

Pathological findings Microscopic examination (Figs 2 and 3) revealed dense infiltration of the corneal stroma by macrophages containing foamy cytoplasm. A few lymphocytes were scattered in each field. The pathological diagnosis was "xanthoma".

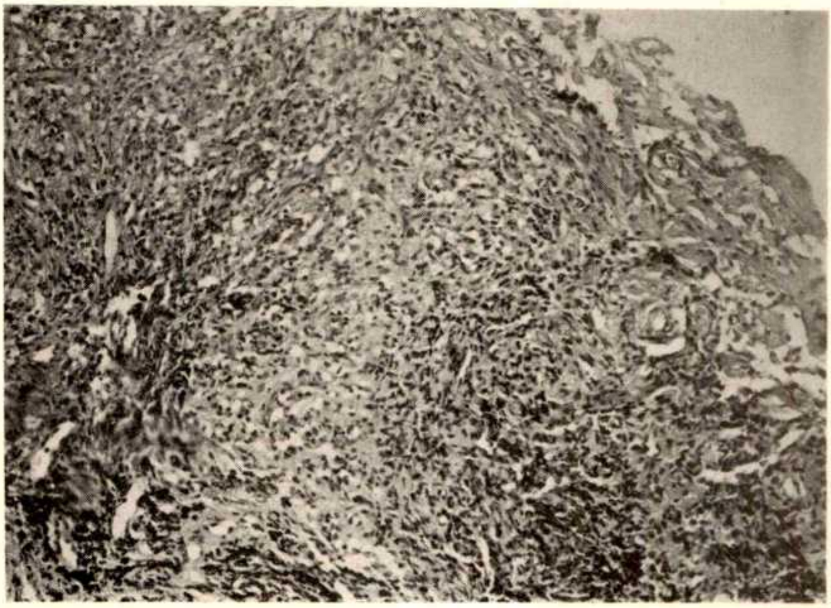

FIG. 2 *Infiltration of cornea with lipid-laden macrophages. Haematoxylin and eosin.* ×50

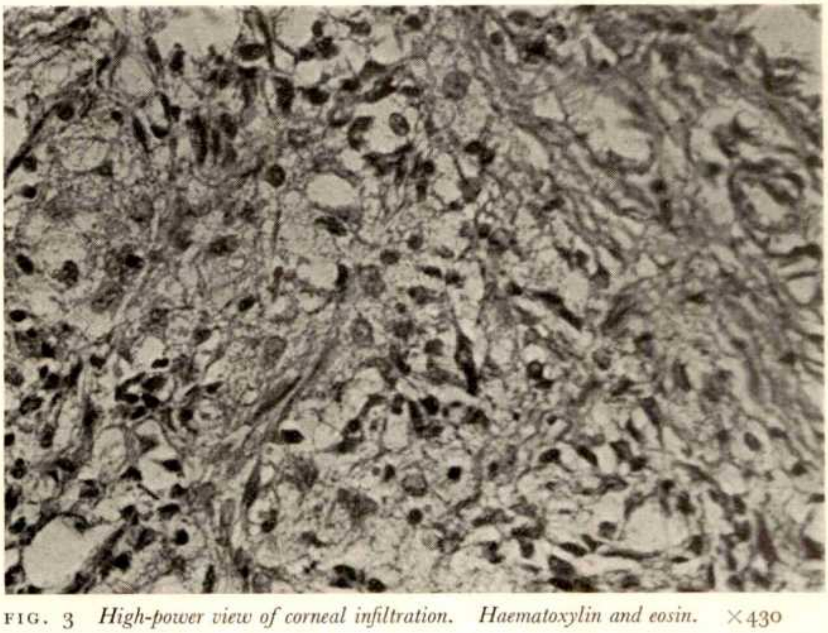

FIG. 3 *High-power view of corneal infiltration. Haematoxylin and eosin.* ×430

Comment

A xanthoma is a nodular mass formed by lipid-laden histiocytes and is usually a manifestation of a group of diseases which are collectively referred to as the xanthomatoses. Thannhauser (1958) has classified the xanthomatoses into the hypercholesteraemic, hyperlipaemic, and normocholesteraemic.

Hypercholesteraemic There is an increase in the total serum cholesterol while the neutral fat remains normal or slightly elevated. This type of lipid abnormality is found in familial hypercholesteraemia, hypothyroidism, and liver disease. The most common lesions associated with this type of lipid abnormality are tuberous xanthomata, plain xanthomata, and xanthelasma formation.

Hyperlipaemic These are associated with an increase in serum neutral fat, but the total lipids may be normal. Hyperlipaemia is found in a familial form, in severe untreated diabetes, chronic pancreatitis, glycogen storage disease, and lipid nephrosis. The clinical picture is that of secondary eruptive xanthoma formation.

Normocholesteraemic These are found in patients with normal lipid values. Duke-Elder and Leigh (1965) mentioned that normocholesteraemic xanthomatoses affected the outer eye in only two conditions—xanthoma disseminatum and Hand-Schüller-Christian disease. Xanthoma formation without apparent metabolic disturbance is also found in eosinophilic granuloma and Letterer-Siwe disease (Liebman, Crocker, and Geiser, 1966; Kara, 1957), in Neiman-Pick and Gaucher's disease (Albert and Smith, 1968), in juvenile xanthogranuloma (Sanders, 1962; Zimmerman, 1965), and in postinflammatory sclerosing lipogranuloma. The above mentioned examples of normocholesteraemic xanthomatosis have typical findings on either physical or radiological examination and were excluded in our patient.

Summary

A unique case of solitary xanthoma of the limbus is presented. No association with trauma, inflammation, lipid abnormality, or systemic xanthomatosis could be found.

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Rhinosporidium granuloma of the conjunctiva with scleral ectasia

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Ocular lesions due to *Rhinosporidium seeberi* are not common in India. The affection is predominantly one of the mucous membranes of the nose and nasopharynx, but occasionally other structures, such as the conjunctiva, lacrimal sac, lids, etc., may be affected (Kuriakose, 1963; Karunaratne, 1964a, b). The infection is usually limited to the surface epithelium, but in rare cases it becomes systemic (Agrawal, Sharma, and Shrivastava, 1959) and the parasite can then be found in any part of the body.

The present paper presents a case of *Rhinosporidium* granuloma of the conjunctiva with ectasia of the sclera probably of the same aetiology. This is the second recorded case of scleral involvement in rhinosporidiosis in the world literature.

Case report

A young male office worker aged 27 years came to the ophthalmic out-patient department of JIPMER Hospital complaining of irritation and fleshy growth in the left eye for the last 2 years. He had also observed a bluish painless swelling near the same site for 20 days. There was no history of injury, and no past history of excision of the swelling was available.

Ocular examination

The cornea, anterior chamber, iris, and pupil of the left eye were normal. About 16 mm. below and temporal to the limbus, partially concealed by the lower lid, there was a bluish, circular cystic swelling (Fig. 1) bulging from the sclera. The swelling measured 10 mm. in diameter and was covered by the conjunctiva. The cyst did not appear to be fixed to the underlying sclera. Trans-illumination showed that it contained clear fluid, and the base had a bluish hue on examination in the slit-lamp beam.

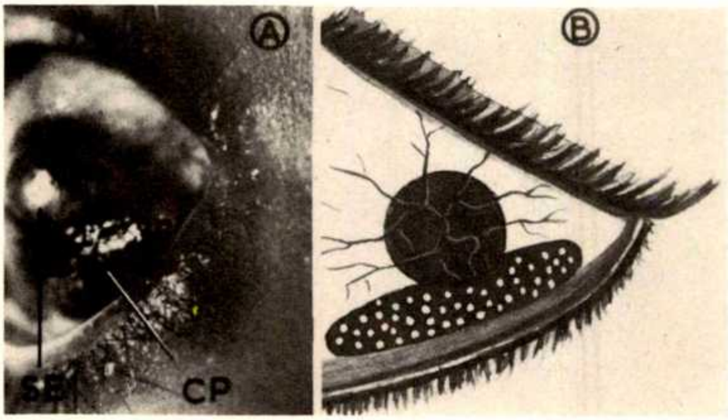

FIG. 1 (A) *Conjunctival polyp (CP) and scleral ectasia (SE). The patient was looking upwards and inwards*

FIG. 1 (B) *Diagrammatic representation of area involved*

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Adjacent to this swelling, occupying the temporal part of the lower fornix, there was a papillomatous lesion with a broad base lying 3–4 mm. above the inferior fornix. The polyp was fleshy with greyish-white granular spots scattered over the surface, and bled at the slightest trauma. The patient's visual acuity was 6/6 with + 1·5 D cyl., axis 90°. The intraocular pressure was normal (18·5 mm. Hg with 5·5 g. weight). Ophthalmoscopy revealed that the optic disc and retina were normal with no evidence of elevation, degeneration, or hole formation (special care was taken to search for any fundus lesion opposite to the external scleral lesion).

The right eye was normal.

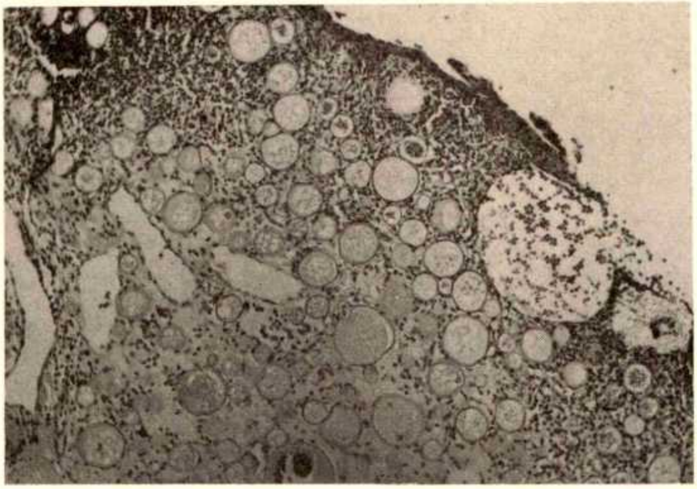

FIG. 2 *Biopsy from conjunctival polyp, showing multiple sporangia in subepithelial layers. Haematoxylin and eosin.* ×40

Investigations

The routine haematological investigations gave normal results. Stools showed no ova or cysts. *X* ray of the chest showed no evidence of intrathoracic suppuration. A conjunctival biopsy from the polyp showed the characteristic lesion of rhinosporidiosis (Fig. 2). A number of sporangia of various sizes were seen in the oedematous subepithelial tissue. The larger ones containing a number of sporangia burst on the surface and the surrounding tissue showed granulomatous reaction with giant cells and mononuclear cells.

Treatment

The conjunctival polyp was widely excised from its base by one of us (P.A.L.), and the bleeding vessels were cauterized. To expose the sclera, the conjunctiva and Tenon's capsule were incised with scissors. The bulge in the sclera was gently aspirated with a 23-gauge needle. After watching for 10 minutes, there was no tendency for the cystic swelling to fill up. A small nick was made in the thin scleral coat in an attempt to excise the cyst when the underlying choroid was observed bulging through the opening. The diagnosis of ectasia and thinning of the scleral coat was established. After diathermy application, preserved homologous sclera (13 mm. in diameter) was grafted over the defect in the patient's sclera. There were no complications and the conjunctival wound was closed.

Result

Postoperatively the patient showed no untoward reaction to the grafted tissue and the graft was well retained. The patient's condition was satisfactory on discharge after 2 weeks with no evidence of infection or ocular inflammation (Fig. 3). He was followed for 12 weeks and showed no evidence of ectasia at the original site. The visual acuity remained at the preoperative level. The retina was normal with full visual fields.

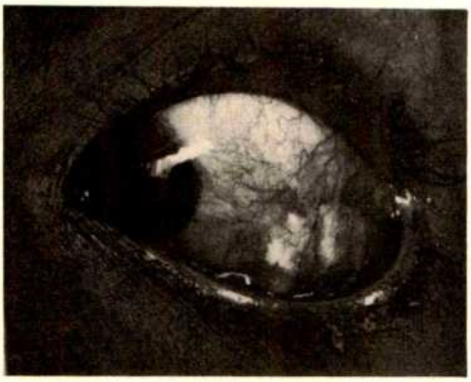

FIG. 3 *Postoperative appearance after 12 weeks*

Discussion

Mycotic infections of the eye are more often recognized in recent years as our knowledge of the various mycoses increases. Rhinosporidiosis is endemic in India and Ceylon, but sporadic cases of infection of the eye have been reported from other countries (Karunaratne, 1964a). The mode of infection is an intricate question, since all attempts to isolate the fungus or to produce the lesions in experimental animals have been fruitless. The published reports on the disease by workers in India, notably Allen and Dave (1936), Mandlik (1937), and Bhaskara Reddi (1954), suggest that contact with infected persons or infected water or soil may spread the disease. Males are affected more often than females in the ratio 9 : 1 (Karunaratne, 1964b).

Site of lesions (Table)

In most reported cases the lesions appeared in the nose and nasopharynx, ocular lesions coming next in frequency. The Table shows the frequency of involvement of various sites based on the analysis of 93 cases reported from India since 1900. Involvement of the sclera in a circumscribed scleral staphyloma was reported in only one case (Kuriakose, 1963). In our patient the scleral lesion simulated a staphyloma, but it was actually an ectasia due to scleral thinning, probably of similar aetiology to the conjunctival polyp. Both these patients retained 6/6 visual acuity, though the scleral ectasia was expected to rupture at any time and cause the loss of the eye.

Table *Involvement of various sites in 93 cases of oculosporidiosis*

Site	*No.*	*Per cent.*
Conjunctiva	31	33
Lacrimal sac	36	39
Canaliculus	1	1
Lid	8	9
Sclera	1	1
Not recorded	16	17
Total	93	100

The diagnosis of the condition is usually based on clinical and histopathological findings. The lesions are essentially chronic granulomata with characteristic sporangia. In an unstained wet preparation, which shows the sporangia, special staining with Alcian blue demonstrated the *Rhinosporidia* as brilliant blue circles (Narayana Rao, 1963).

The conjunctival polyp should be widely excised under surface anaesthesia, but even so recurrences are common. The repair of the scleral ectasia posed the problem of perforation and loss of the eye. The idea of using a preserved homologous scleral graft for repair was derived from the increased use of such grafts in retinal detachment surgery (Wilson, 1964) and in cases of scleromalacia perforans. In the present case, the recipient ocular tissue has shown good tolerance of the preserved scleral graft for 12 weeks with no evidence of infection.

Summary

A second case of *Rhinosporidium* granuloma of the conjunctiva with scleral ectasia is reported. The scleral defect was repaired with a preserved human scleral graft with satisfactory results.

Our thanks are due to Dr. K. Chandra, M.D., Professor of Pathology, JIPMER, for the histopathological report. We are also grateful to Dr. M. Balasubramanyan, M.D., Principal of the Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, for permission to publish this article.

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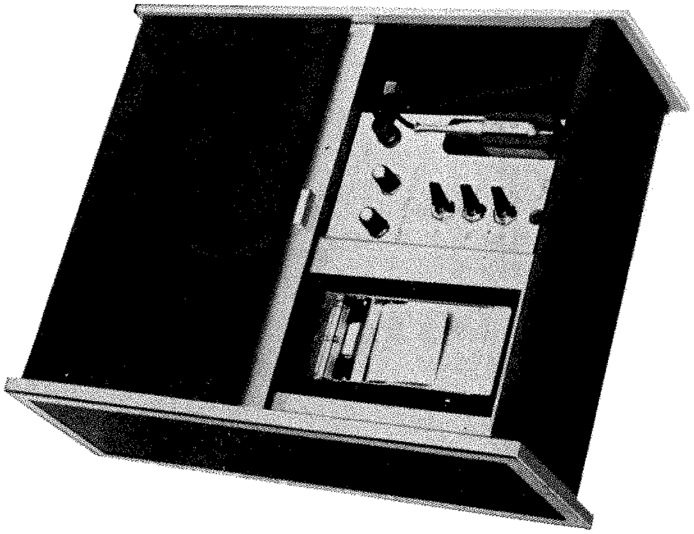

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Staining of experimentally-induced chorio-retinal lesions with Disulphine blue and Evans blue

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It is often difficult to assess the extent and activity of chorio-retinal lesions of inflammatory or surgical nature. Fluorescein angiography has been used with success, but this technique requires a clear media and the use of filters and other elaborate equipment. The development of an alternative simpler technique, using other dyes, to demonstrate increased vascular permeability in chorio-retinal lesions is therefore of clinical interest and forms the subject of this report.

Material and methods

Four albino rabbits weighing 2·5 to 3 kg. were anaesthetized with intravenous pentobarbital sodium.

RABBIT 1

One eye was proptosed and the sclera was exposed posterior to the equator by a semilunar incision in the conjunctiva, from 9 to 3 o'clock. Two diathermy marks, the first stronger than the second, were placed 5 to 6 mm. from one another, at a distance of 8 to 9 mm. from the limbus, thus avoiding the area of the retina containing myelinated fibres. Indirect ophthalmoscopy demonstrated a mild whitish reaction at the site of the weak diathermy application and a more marked area of coagulation in response to the stronger diathermy. Immediately after application of the diathermy, 6·2 per cent. solution of Disulphine blue* (wt./volume) was injected intravenously through the auricular vein (0·5 ml./kg.).

The fundus was examined during the course of the injection and at 2, 5, 15, 30, 60, 120, and 180 minutes, and 24 and 48 hours after the injection. Fundus photography of the diathermized areas was performed before and after the injection of the dye.

RABBIT 2

The same procedure was repeated and cryothermy of −40°C. was applied to the sclera. A mild reaction was obtained by applying the tip of the cryostat to the sclera for a short time until there was a mild whitish reaction on the fundus. A more marked lesion was obtained by applying the cryostat for a longer time until an obvious reaction appeared at the site of application. Both reactions were controlled by indirect ophthalmoscopy.

RABBIT 3

Two photocoagulation marks of different intensity (weak and strong) were produced. The weak reaction was obtained by setting the Zeiss Photocoagulator at 20V and 40A for 1 second and the stronger by setting it at 22V and 45A for approximately 3 seconds.

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*Monosodium salt of anhydro-4 : 4'-bisdiethyl aminotriphenyl methanol-2'' : 4''-disulphonic acid (Sulphan blue). Manufactured by I.C.I., Wilmslow, Cheshire, U.K.

RABBIT 4

Weak and strong diathermy marks were produced as in Rabbit 1, but immediately thereafter 1·5 ml. of 2 per cent. solution of Evans blue (0·5 ml./kg. body weight) was injected intravenously.

Results

In the three rabbits injected with Disulphine blue, the whole fundus became blue within a few seconds. The intensity of the blue stain decreased rapidly and disappeared from all areas other than the injured ones within 1 minute. However, these areas retained a residual light blue colour which increased progressively in intensity during the following 15 minutes. There was no apparent difference in the colour obtained after the application of weaker and stronger stimuli, in the three different procedures used. All the lesions stained homogeneously blue, but the staining was more intense when diathermy and photocoagulation were used than after cryothermy. Figs 1 and 2 show the appearance of a strong photocoagulation lesion before and 5 min. after the injection of Disulphine blue.

One hour after the injection of Disulphine blue, the staining in the lesions began to decrease, and about 2½ hours after the injection the colour disappeared completely. A mild blue flare, which gradually disappeared after 24 hours, was observed in the anterior chamber and in the vitreous. The skin and mucosae of the rabbits stained blue immediately after injection of the dye and the colour disappeared gradually within 36 hours. The urine remained blue for the same length of time.

In Rabbit 4, injected with 2 per cent. Evans blue, the diathermized area showed initial staining 45 min. after the injection. The staining was maximal after 90 min. and was evident for the next 3 days. The skin and mucosae became bluish in colour 12 hours after the injection and remained blue for 3 days.

Discussion

Disulphine blue has been used in humans by plastic surgeons in order to assess the degree of skin burns, which were determined according to the amount of blue staining of the injured areas (Gibson and Brown, 1945; Tempest, 1958). In ophthalmology, Sorsby (1939) first used the dye to establish the extent of retinal detachment and the location of retinal holes. The dye is reported to be nontoxic in humans, and is rapidly excreted by the kidneys, although there is occasional transient nausea.

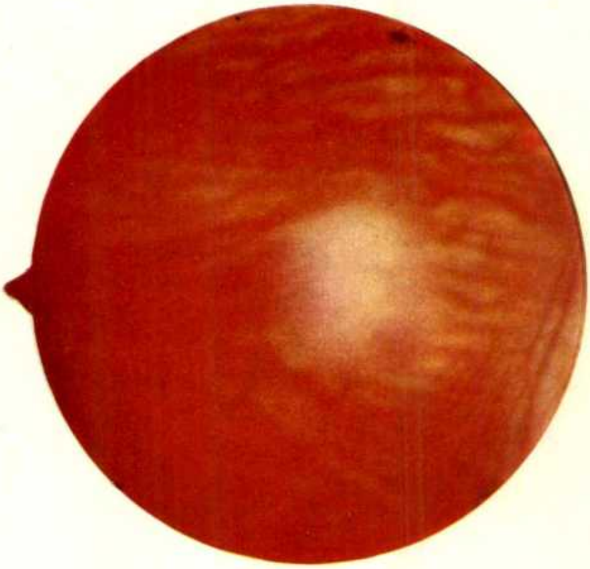
In the present study it has been shown that the dye (0·5 ml./kg.) is capable of staining chorio-retinal lesions, probably by leaking through injured vessels. The intensity of staining was somewhat stronger after diathermy and photocoagulation than after cryothermy. This probably indicates more severe vascular damage in the two former lesions. When Disulphine blue was injected in smaller doses which did not colour the skin, it also failed to stain the chorio-retinal lesions. Evans blue was found to have the same properties, but the staining process was slower and the disappearance of the dye from the skin was more prolonged.

In the light of the above data, the use of these dyes may be of clinical importance in studying chorio-retinal lesions of surgical or inflammatory nature.

Summary

(1) Disulphine blue (0·5 ml./kg.) administered intravenously was used *in vivo* to stain chorio-retinal lesions produced by diathermy, photocoagulation, and cryothermy.

Staining of experimentally-induced chorio-retinal lesions



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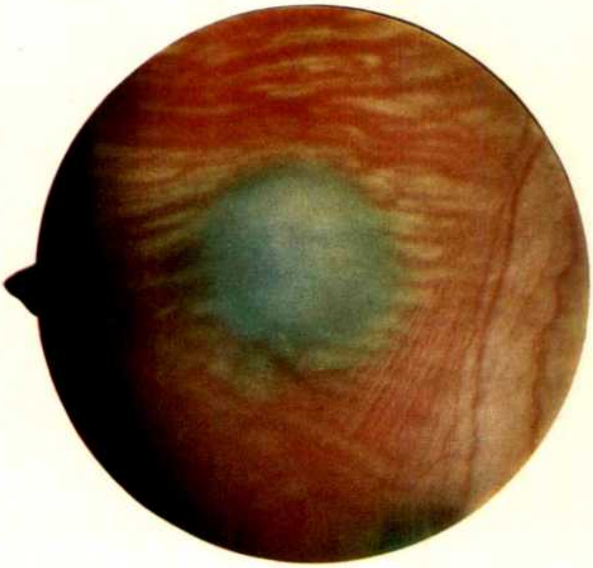

(2)

FIG. 1 *Rabbit* 3. *Fundus appearance of a strong photocoagulation mark*

FIG. 2 *Rabbit* 3. *Blue staining of the same photocoagulation mark,* 5 *min. after Disulphine blue injection*

(2) The above lesions stained homogeneously blue within a few minutes of injection of the dye and retained this colour for a period of approximately 2½ hours.

(3) The main untoward effect of the dye was a diffuse staining of the skin during approximately 36 hours.

(4) A solution of 2 per cent. Evans blue (0·5 ml./kg.) also stained chorio-retinal lesions in a similar manner but more slowly.

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Brit. J. Ophthal. (1970) 54, 572

Book reviews

Recent Research on the Retina. Edited by E. S. PERKINS. 1970. *Brit. med. Bull.*, 26, May, Pp. 99–184.

The May issue of the *British Medical Bulletin*, entirely devoted to recent research on the retina, is of great interest to ophthalmologists, pathologists, and physiologists; Professor Perkins acted as Scientific Editor. The comprehensive introduction is by Norman Ashton, who also contributed the first article on retinal angiogenesis in the human embryo, and a later article on the pathology and physiology of cotton-wool spots. There are papers on the ultrastructure of the retina (Pedler and Young), receptor potentials (Arden), the metabolism of the retina (Graymore), the optical properties of the photoreceptors (Weale), recent work on visual pigments (Dartnall), and their anomalies in colour-defective subjects (Rushton). Fluorescence angiography is described in general terms (Hill) and particularly in diabetic retinopathy (Kohner and Dollery). The pathology of diabetic retinopathy is discussed by Garner, its experimental production by Heath, and the management of oxygen therapy to premature infants to prevent the development of retrolental fibroplasia by Baum and Tizard. The lesions produced by laser irradiation are described by Marshall and Mellerio. Comparative studies are also included, of deep-sea fishes (Locket) and of the avian retina (Cowan).

The subjects are well chosen, for in each there has been much fundamental research in the last decade, producing results of unusual interest and importance. All the contributors are acknowledged authorities on their various subjects and, as would be expected, the articles are unusually good. This issue of the *Bulletin* is beautifully illustrated and is well worth reading.

Occupational and Medicative Hazards in Ophthalmology (III Congress of the European Society of Ophthalmology, Amsterdam. 1968). Edited by J. FRANÇOIS. 1969. Pp. 722, 211 figs, bibl. Karger, Basel. (£15)

This volume contains reports of the proceedings of the 3rd Congress of the European Society of Ophthalmology, which was held in Amsterdam in 1968. The majority of the papers are concerned with ocular injuries resulting from industrial processes or from environmental conditions such as high altitude, ultra-violet light, and even space travel. Electrical injuries, chemical burns, the problems of visual fatigue, and methods of prevention of industrial injuries are described. Numerous papers describe the ocular changes resulting from treatment with drugs such as chloroquine.

It is difficult to single out papers for individual mention from the 83 presented, particularly as many of them are reviews or summaries of previous work. Most ophthalmologists will find articles of interest in this volume and it should certainly be consulted by those who are concerned with industrial ophthalmology.

The book is well produced and there are English summaries of the papers.

The Eye. Vol. 1. Vegetative Physiology and Biochemistry. Edited by H. DAVSON. 2nd ed., 1969. Pp. 679, figs, bibl. Academic Press, New York and London. ($26)

We are all indebted to Dr. Davson and his collaborators for the second edition of this volume, which originally appeared in 1962. One chapter which was contained in the first edition (on comparative anatomy of the vascular supply) has been omitted, but the remainder have all been revised and largely re-written, and there is an entirely new chapter on "General Aspects of Retinal Metabolism" by C. N. Graymore. The other major addition is a chapter on "The Lens: Function and Macromolecular Composition" (S. G. Waley), "Lenticular Metabolism and Cataract", as before, being dealt with by R. van Heyningen. The remaining chapters are "Gross Anatomy and Embryology" (P. C. Kronfeld); "Intraocular Fluids" and "Intraocular Pressure" (H. Davson); "Vitreous Body" (A. Pirie); and "Cornea and Sclera" (D. M. Maurice).

Like Mr. Weller's knowledge of London, Davson's contributions to the physiology of the eye are "extensive and peculiar". Their extent is obvious; their peculiarity is perhaps only appreciated by considering who else would undertake such an integrated account (in the first place), be able to collect such a team of authoritative contributors, and persuade them all to revise and update their texts to produce this excellent volume.

Atlas of Diagnostic Techniques and Treatment of Intraocular Foreign Bodies. By W. H. HAVENER and S. L. GLOECKNER. 1969. Pp. 197, 90 plates. Mosby, St. Louis; Kimpton, London. (£8 15*s*.)

This excellent book is similar in format to that produced in 1967 by the same authors dealing with the diagnosis and treatment of retinal detachment. The text has been clearly written and is profusely illustrated with line drawings, the number of which no doubt contributes to the high cost of this book.

The first part deals with diagnostic techniques, including slit-lamp microscopy, gonioscopy, use of the three-mirror lens, the electric locator, ultrasonic techniques, and radiological localisation by the method of Sweet, but there is no mention of the prognostic and medico-legal importance of recording the visual acuity. The main emphasis in this section is on the use of the indirect ophthalmoscope, with scleral depression, with a detailed account of the principles and techniques of this procedure. In the second part there is a comprehensive description of the surgical techniques available for removal of foreign bodies from different sites within the globe and the importance of prophylactic measures (particularly cryotherapy) to prevent subsequent retinal detachment is stressed. This section is liberally illustrated and contains many useful surgical tips.

This atlas can be highly recommended and should certainly be available for the use of ophthalmic residents; those who are faced only occasionally with an intra-ocular foreign body might well find it helpful.

Fundamentals of Visual Science. By M. L. RUBIN and G. L. WALLS. 1969. Pp. 435, 71 figs, 90 refs. Thomas, Springfield, Ill. ($17.50)

This interesting book deals with the perception of light and space. It is written in a conversational style which may be initially irritating (but this soon passes), and the format suggests that it is derived from a series of physiology tutorials, the whole approach being physiological rather than clinical. The contents cover the nature of light, entoptic phenomena, photochemistry, electrophysiology, assessment of visual acuity, colour vision, and spatial vision. Several features make the book particularly attractive. The experiments are described critically where necessary and the reader is given a feeling of involvement. The references are well selected and it is evident that in many cases the authors know the workers, and their laboratories, which also adds to the personal interest.

For a clinician it may not be an easy book to read and, in view of the way it is written, it is difficult to go back to re-read certain parts as required. The discussion of spatial vision is prefaced by a glossary of terms to be used to avoid ambiguity. This book can be recommended to every ophthalmologist, and particularly to the candidate for the fellowship or other higher examination.

Structure of the Uveo-Trabecular System (Über die Struktures Uvea-Trabekel-Systems.) By L. VALU. 1970. Pp. 69, 54 figs, refs. Thieme, Leipzig (Abhandl. Augenheilk., vol. 38). (DM 18.50)

The author gives a detailed description of the structure of the trabecular system of the anterior chamber angle as ascertained by histology, histochemistry, polarization, and electron microscopy.

The arrangement of the collagenous and elastic fibres will interest the anatomist more than the ophthalmic clinician. The ophthalmic surgeon may want to learn about the influence of a greater or diminished trabecular outflow resistance on the production and chemistry of the aqueous, or about the influence of a trabecular scar after a von Graefe knife section and iridectomy, but these matters are not considered. Senile changes of the tissue fibres are discussed, and the author also mentions that, in cases of absolute glaucoma, the trabecular network is found to be transformed into a coalescent hyaline mass. The action of pathological conditions on the trabecular tissue deserves more detailed treatment.

Laser Photocoagulation and Retinal Angiography with Current Concepts in Retinal and Choroidal Diseases. By H. C. Zweng, H. L. Little, and R. R. Peabody. 1969. Pp. 297, 283 figs, 3 col. pl., refs. Mosby, St. Louis; Kimpton, London. (238*s*.)

This book is intended to help the practising ophthalmologist in his everyday work. In this regard it is an excellent summary of present concepts in dealing with macular disease, the accompanying fluorescein angiograms and photographs being of a high quality. Although there is an opening section on lasers in general, most of the chapters dealing with the clinical work are confined to use of the ruby laser. The effects of this instrument in macular disease are particularly impressive, and the authors continue their policy of cautious optimism.

This book has been published only at the dawn of work with the Argon continuous wave laser, and although this instrument is mentioned the authors have had little opportunity to include their results with it.

The number and quality of the pictures are admittedly high, but the book is extremely expensive.

Symposium on Ocular Therapy. Volume 4. Edited by I. H. Leopold. 1969. Pp. 145, 13 figs, bibl. Mosby, St. Louis; Kimpton, London. (126*s*.)

The book presents, with certain additions, the information presented at the Drug Symposium of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology joint meeting in Chicago in 1968.

There are chapters on drug metabolism, management of conjunctival disorders, effect of Phospholine Iodide on anterior chamber depth, the lens, problems of carbonic anhydrase inhibitors, topical corticosteroids, lens changes and Phospholine Iodide, ocular toxicity of systemic drugs, therapy of retinal vascular occlusions, drug-induced pseudo-tumour cerebri, drug therapy in uveitis, antibiotics in ophthalmology, and sedation of children.

The opening chapter by Leopold, who has edited the whole book, presents much fascinating data, particularly on the genetic aspects of human responses to drugs; it is written in a masterly fashion as one would expect from this author. Chapter 2, also by Leopold, is a classic which should be required reading by every ophthalmologist. It deals with the causes of surgical infections, their management and prophylaxis, with a magnificent account of the characteristics, side-effects, dosage schedules, and even prices of practically all known antibiotics; anti-fungal therapy is also covered in this chapter.

The rest of the book is a mixed bag of shortish statements on the standard facts of pharmacology and therapeutics in various clinical situations and on a variety of therapeutic agents; original articles on particular facets of drug action or toxicity (such as for example the cataractogenic features of Phospholine Iodide, dealt with in two separate chapters); and a general account of recommended procedures in evaluating the safety of a new drug.

It is obvious that the proceedings of a symposium published in book-form cannot be, and are not intended to be, a complete text on the subject concerned. In this the present volume is no exception. But there is no denying the wealth of information useful to the clinician which it contains.

Microsurgery in Glaucoma. Advances in Ophthalmology, Vol. 22 (*Bibliotheca Ophthalmologica*, No. 81.) Edited by G. MACKENSEN. 1970. Pp. 287, 140 figs, bibl. Karger, Basel. (196*s*.)

This book contains the proceedings of the Second Symposium of the Ophthalmic Microsurgery Study Group held in June, 1968, at Burgenstock, Switzerland. The title does not quite indicate the contents since, in addition to detailed discussions on microsurgery in glaucoma, there is also excellent material concerning many other aspects of microsurgery. There is a section on the "hardware" and "software" of microscopy, in which surgical instruments, the microscopes themselves, and suture materials are fully discussed.

Furthermore there is much valuable material on microsurgery in cataract, trauma, and keratoplasty, including a most detailed and valuable section on the niceties of graft suturing. A chapter dealing with the anatomical and pathophysiological aspects of glaucoma includes a typically brilliant contribution by Goldmann.

Two short sections on neurology and ocular circulation, although of merit, stand out as curiously irrelevant in this particular book.

The most important chapter from the point of view of advances in ophthalmology is the third, in which several authors describe their experiences with new methods of glaucoma surgery, trabeculotomy, sinusotomy, etc. Krasnov, who presented a vast number of cases but who seems to take a curiously oversimplified view of the aetiology of glaucoma, described his methods in detail. His ingenuous statement that "the differential diagnosis between 'intra-scleral' and 'trabecular' glaucoma is finally settled during the operation itself at the moment of reaching Schlemm's canal" (by seeing how much fluid is leaking through the trabecular meshwork) had to stand up to some pretty close questioning from the other members of the symposium.

Harms and Dannheim combined the removal of a small oblong of scleral wall with an extensive trabeculotomy to either side of it. They stressed the low complication rate.

Linnér found early closure of simple trabeculotomy unsatisfactory (other evidence for this is also presented) and now does a modified Cairns procedure.

Cairns gave a commendably clear description of his operation with beautiful diagrams and again stressed the low complication rate.

Other chapters include a valuable appraisal of the worth of the microscope in ordinary glaucoma procedures; the chapter containing a discussion of glaucoma surgery makes fascinating reading.

This book can be highly recommended to all ophthalmologists and is essential reading for anyone interested in the subject of glaucoma. The editors may be congratulated on a polished production.

Aspects of Developmental and Paediatric Ophthalmology. Clinics in Developmental Medicine, 32. Edited by P. GARDINER, R. MACKEITH, and V. SMITH. 1969. Pp. 128, figs, bibl. Spastics International Medical Publications, London. (42*s*.)

This valuable publication comprises the edited version of the proceedings of a symposium on paediatric ophthalmology which was held in Birmingham in April, 1968, under the joint auspices of the Royal National Institute for the Blind and of the Spastics Society. In view of this sponsorship it was natural that there should be an emphasis on the significance of visual handicaps associated with other physical or mental disorders, and on the medical and social aspects of the management and education of children with multiple handicaps. There are excellent short sections on the physiological and psychological aspects of the development of visual perception and on the assessment of vision in very young or handicapped children. It is demonstrated that refractive errors are much more common in the presence of a mental handicap in childhood and the importance of correcting visual defects in deaf children is emphasized; these and other associations of visual disorders in childhood are the basis of the important concept of the "at risk" pre-school-age population in terms of visual screening procedures.

Short sections concerned with important ocular disorders presenting at birth or in early childhood are aimed particularly at paediatricians, child welfare officers, teachers, and other lay personnel who are intimately concerned with the upbringing and education of visually handicapped children. The fact that both the audience and the participators at this Symposium were from widely differing disciplines is both the strength and the weakness of this book from the ophthalmologist's point of view. The emphasis on the broader significance of visual handicap in the management of the "whole" child is extremely important for him to appreciate; on the other hand, the purely ophthalmic aspects have had of necessity to be presented in an over-simplified fashion. The greatest value of inter-disciplinary meetings of this type lies in the discussions which follow the formal presentation of papers, and it seems a great pity that the editors have not included at least the important points from such discussions in the book. It is the differing emphasis which the ophthalmologist, the paediatrician, the educational psychologist, the welfare worker, and the teacher put on various aspects of management of the visually handicapped child in the light of their experience which is of the greatest value in demonstrating the absolute necessity of a team approach to the problem, and this is often inferred rather than directly demonstrated in this book. Nevertheless, the publication will prove of great value to those who have concern for all aspects of paediatric ophthalmology.

Notes

Library Association and National Association for the Education of the Partially Sighted

Conference, October 28, 1970

A one-day conference on print for the visually handicapped reader will be held at the Commonwealth Hall, Royal Commonwealth Society, 16 to 20 Craven Street, London, W.C.2., on Wednesday, October 28, 1970. Additional information may be obtained from the Research Officer, The Library Association, 7 Ridgmount Street, London, WC1E 7AE.

Seminar on Clinical Echo-ophthalmography

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A Seminar on Clinical Echo-ophthalmography will be held at the II Ophthalmology Service (Head: Prof. Dr. J. Boeck), University of Vienna Medical School, Austria, on October 12 to 16, 1970.

For further information and registration, please write to: Dr. Karl Ossoinig, c/o II Ophthalmology Service, University of Vienna Medical School, Alserstrasse 9, A-1090 Vienna, Austria.

Symposium on Retinal Surgery

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The Retinal Unit, Moorfields Eye Hospital, City Road, will hold a symposium for consultants on the Diagnosis, Treatment, and Complications of Retinal Detachment and Allied Conditions at the Moorfields Annexe, Highgate, from Thursday, 26 November, at 7 p.m., to Saturday, 28 November, at 3 p.m. Cases will be shown and the techniques used in this Unit will be demonstrated. Controversial aspects of this subject will be discussed at a Panel Discussion at Kenwood House.

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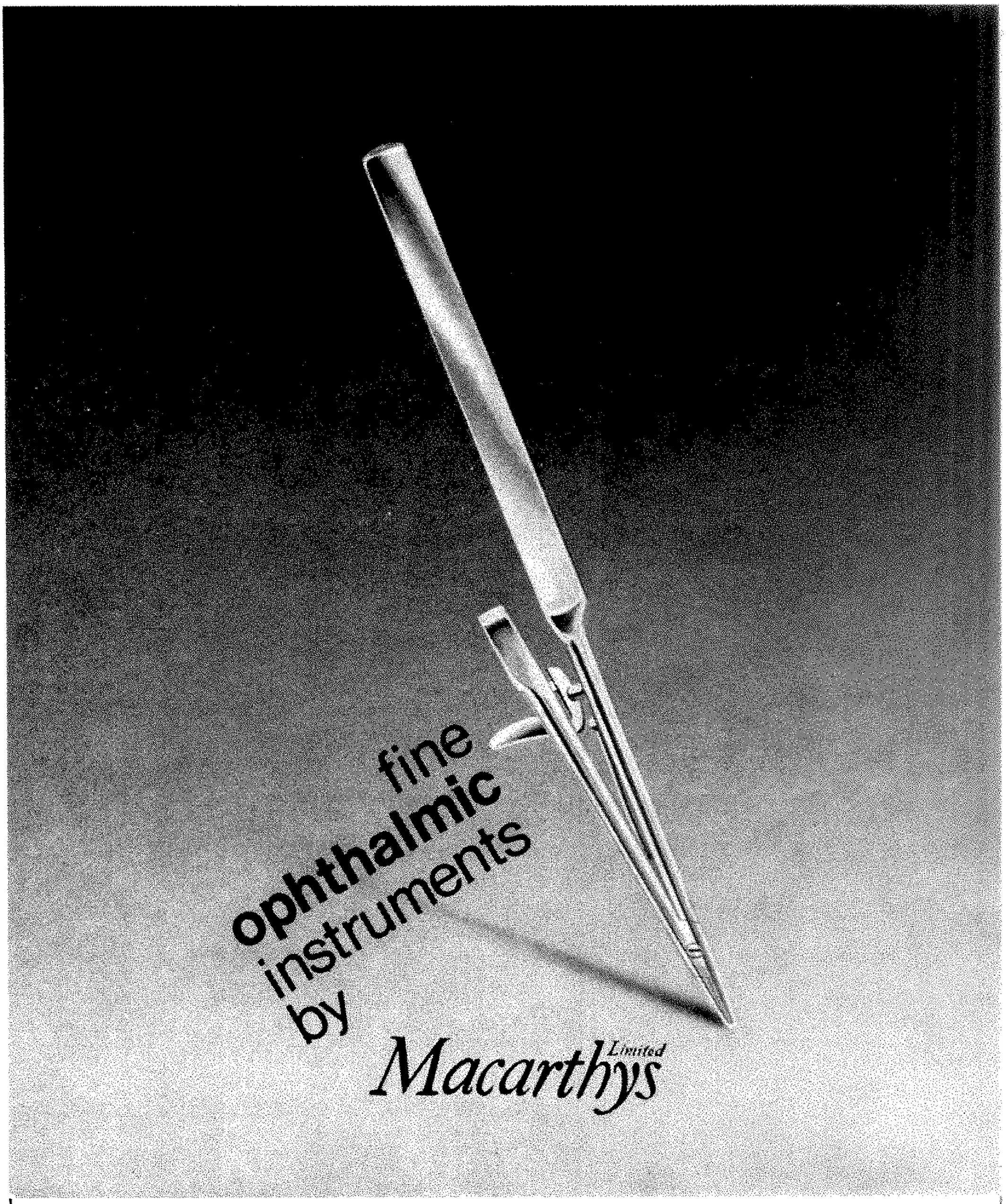

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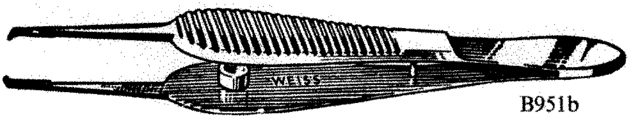

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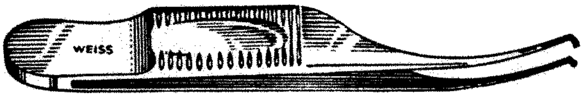

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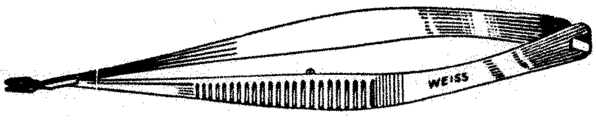

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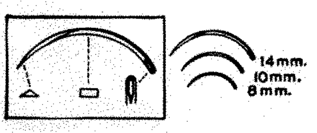

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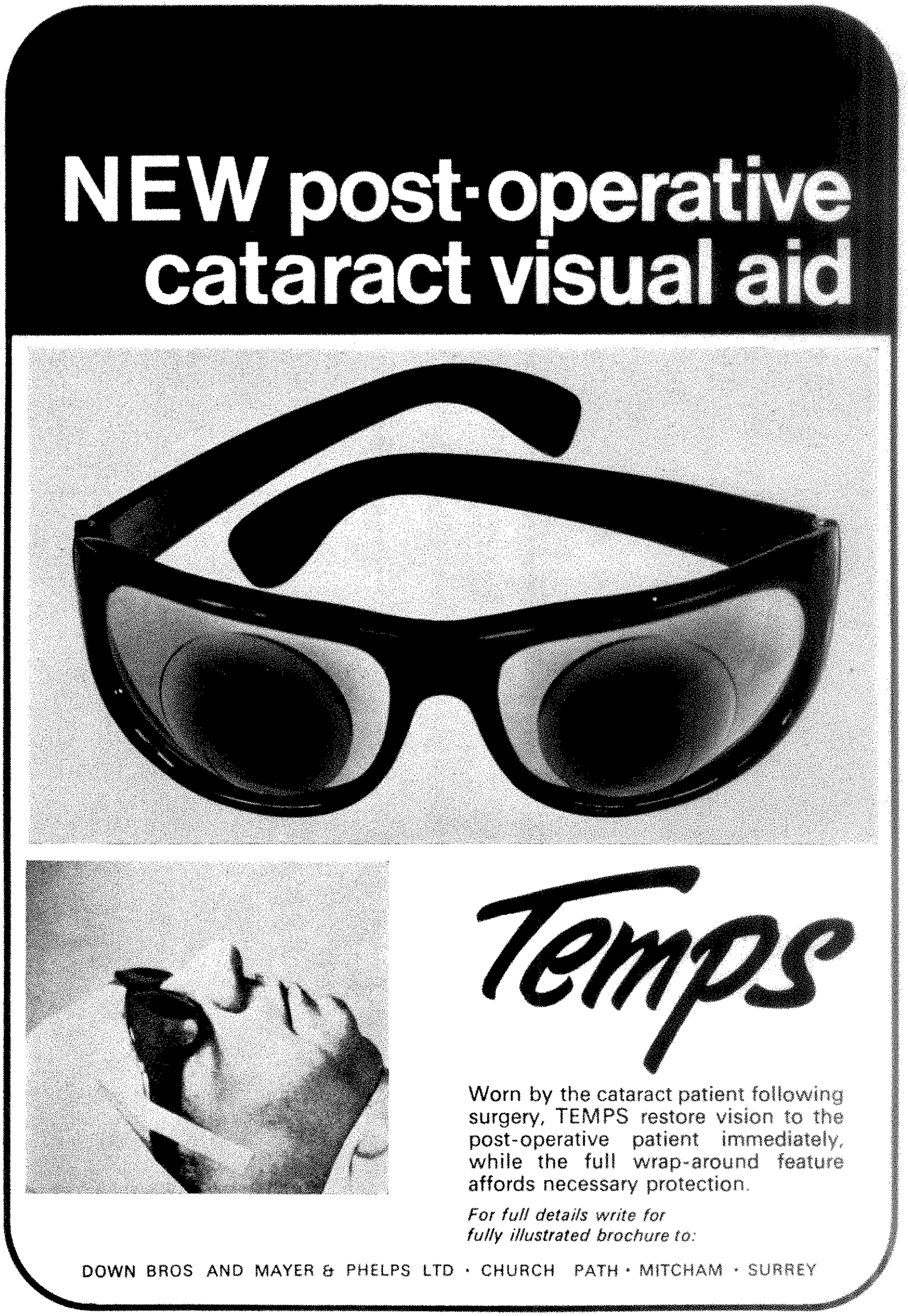

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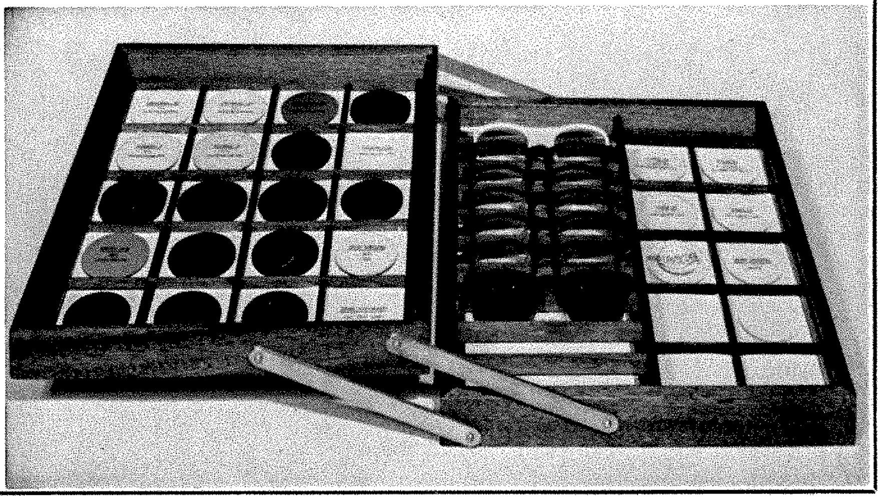

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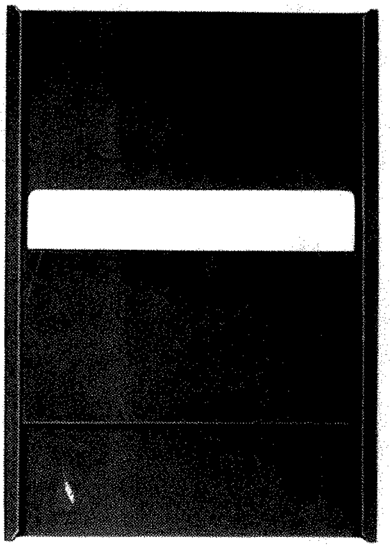

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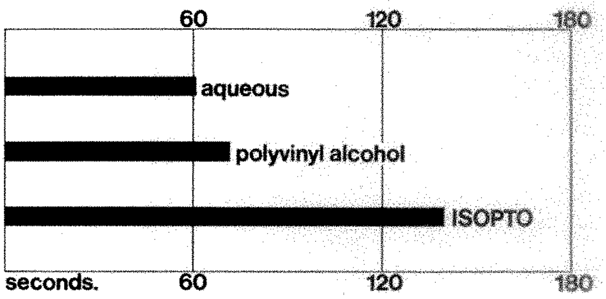

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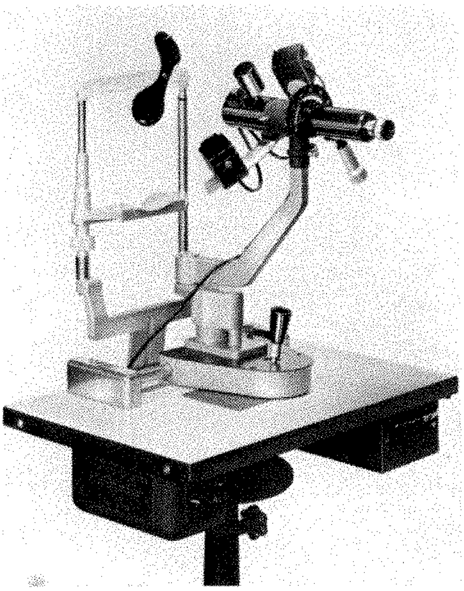

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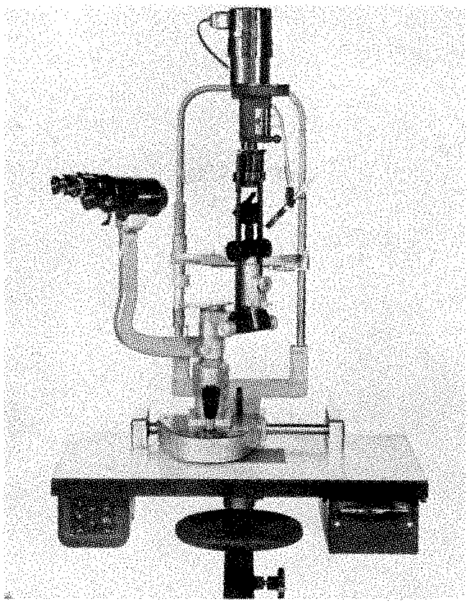

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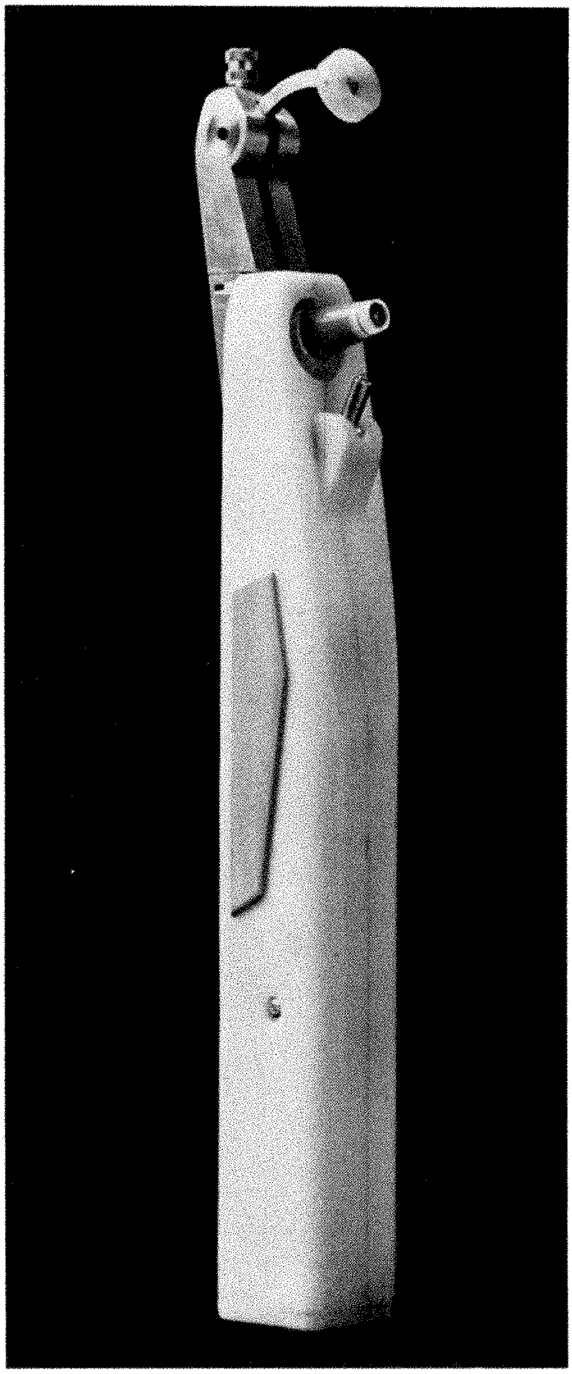

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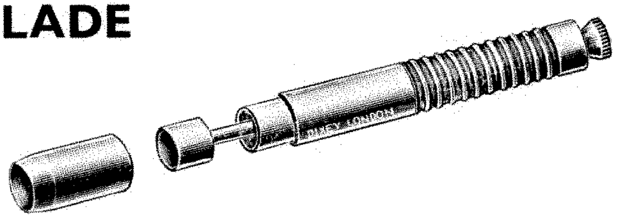

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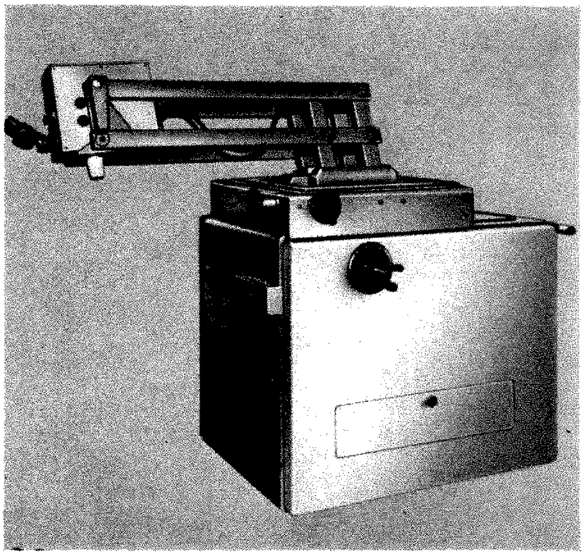

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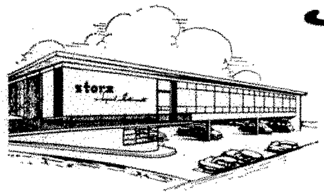

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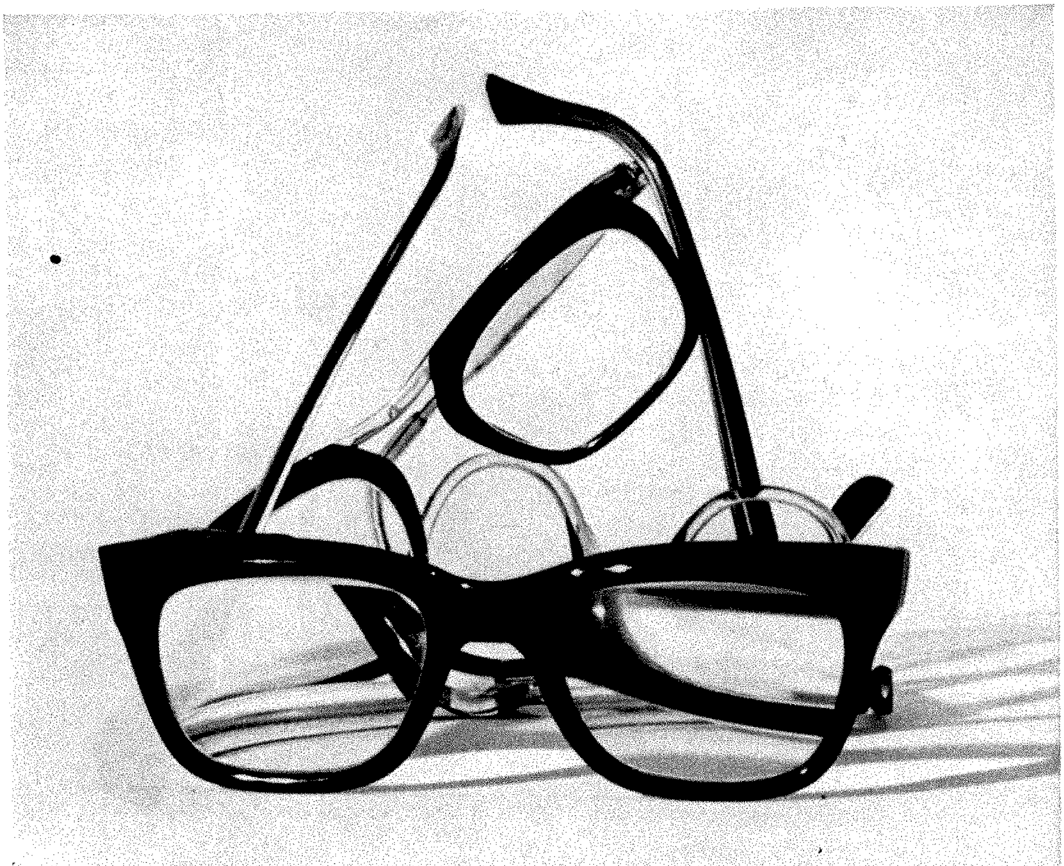

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Communications

Corneal anaesthesia after alcohol injection of the trigeminal sensory root

Examination of 100 anaesthetic corneae

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It is well known that lesions affecting the trigeminal nerve may lead to the development of neurotrophic keratitis (Magendie, 1824), but the incidence and the extent of the keratitis seen by biomicroscopic examination of the cornea, and in particular its effect upon visual acuity, are not well documented. The present study was undertaken to investigate these aspects of keratitis, in corneae rendered anaesthetic by alcohol injection of the trigeminal sensory root (henceforward referred to as Injection) (Penman and Smith, 1950; Penman, 1958).

Selection and examination of patients

97 patients were examined, 94 of whom had tic douloureux, and three migrainous trigeminal neuralgia. Three of the patients with tic douloureux had received bilateral Injections, making a total of 100 anaesthetic corneae. 86 of the patients were seen at Atkinson Morley's Hospital, and the other eleven came from the National Hospital for Nervous Diseases. Their ages at the time of examination ranged from 31 to 86 years, the majority (44 patients) being in the age group 60 to 69 (Table I). Females outnumbered males by 71 to 26, and right eyes outnumbered left by 72 to 28; these figures are in keeping with those for tic douloureux. Four patients suffered from disseminated sclerosis, the association of which with tic douloureux is well recognized, and one patient had syringomyelia which is also known to occur with tic douloureux; no other neurological disease was present, nor was any patient suffering from any relevant systemic illness.

Table I *Age and number of patients*

Age (yrs)	*No. of patients*
30–39 (youngest 31)	4
40–49	6
50–59	21
60–69	44
70–79	17
80–89 (oldest 86)	5
Total	97

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Before Injection 45 patients had received treatment with Tegretol (carbamazepine) (Campbell, Graham, and Zilkha, 1966) for a time, either until the drug no longer alleviated their symptoms, or until they were forced by side-effects to discontinue it. A few had undergone unsuccessful surgery at an earlier date; in most cases this had been a peripheral neurectomy, but one patient had undergone a craniotomy. Cervical sympathectomy had been performed on one man 17 years earlier in an attempt to relieve his tic douloureux.

The length of time since Injection ranged from one month to 20 years, the largest group of patients (25) being seen after 5 years (Table II). The reason for this relatively large number seen at 5 years was that this was the last time patients were seen routinely for follow-up after Injection.

Table II *Number of eyes and time since injection*

Time since injection	*Months*				*Years*														*Total eyes*
	Less than 1	1–3	3–6	7–11	1	2	3	4	5	6	7	8	10	11	12	13	18	20	
No. of eyes	10	2	13	5	17	12	1	1	25	4	2	1	2	1	1	1	1	1	100

Patients were examined when they attended the neurological outpatients department for routine follow-up after Injection. The criterion for inclusion in the study was that corneal sensation should be entirely absent; any patient with partial anaesthesia of the cornea was excluded. Initially an attempt was made to assess from the patient any ocular complications that occurred soon after the Injection, but this did not prove practicable, as in many cases Injection had been performed years previously, and any treatment required had been carried out at the patient's local hospital. It was therefore decided to record only the present or periodic symptoms and signs of which the patient complained. It was established that none of the patients had had previous tarsorrhaphies which had subsequently been opened.

Ocular examination

The visual acuity was recorded, and compared with that before Injection (in the great majority of patients this had been noted). A standard Schirmer's test was then carried out on both eyes simultaneously for 5 minutes, using a No. 1 filter paper. By this means the normal eye was used as part of the afferent pathway, to test the integrity of the afferent pathway on the normal side, and also to compare the resultant lacrimation on the two sides. Rowbotham (1939) emphasized that the greater superficial petrosal nerve may be damaged at the time of Injection. This was followed by an examination of the cornea and anterior segment with the slit-lamp microscope, which included staining of the corneal epithelium with fluorescein. Finally corneal sensation was tested using a Cochet-Bonnet aesthesiometer. With the patient seated at the slit lamp, the nylon thread was applied to the cornea at five points; at the centre, and 2 mm. from the limbus at the 12, 3, 6, and 9 o'clock meridians. Anaesthesia was considered to be complete if the patient was unable to feel indentation of the cornea by the nylon thread at a length of 5 mm.

Results

These were classified according to the visual acuity and the presence or absence of keratitis:

Group 1 No keratopathy.

Group 2 Evidence of keratopathy but good visual acuity.

Group 3 Keratopathy resulting in impairment of vision.

Group 1 (75 eyes)

(*a*) *Visual acuity and examination of the cornea*

There was no evidence of keratitis at the time of examination, and apart from four eyes visual acuity was 6/12 or better; forty (54 per cent.) saw 6/6 or better, seventeen (23 per cent.) saw 6/9, fourteen (19 per cent.) saw 6/12. The remaining four eyes in which the vision was less than 6/12, showed other ocular disease, namely gross macular disturbances in two, advanced crystalline lens changes in one, and advanced tapeto-retinal degeneration in the fourth.

(*b*) *Tarsorrhaphy*

Four patients in this group had had lateral one-third tarsorrhaphies; it must be presumed that at some stage it had been considered necessary to carry this out. In the first patient (male, 59) it had been done 2 weeks after Injection, which had been performed 6 months previously. The second (female, 70) had been Injected a year earlier; tarsorrhaphy had been carried out only 2 weeks before she was examined but her cornea was entirely normal. Injection of the third patient (female, 50) had been performed 7 years previously, and tarsorrhaphy 3 years after Injection. The fourth patient (female, 50) had undergone tarsorrhaphy within a month of Injection carried out 7 months earlier.

Except for the second patient the tarsorrhaphies could probably be gradually opened.

(*c*) *Symptoms*

The only ocular complaints of patients in this group were few and non-specific, and were usually related to dysaesthesiae which not infrequently follow trigeminal denervation.

(*d*) *Schirmer's test* (*Tables III and IV*)

Table III shows the Schirmer readings from the control (normal) eyes, and Table IV the readings from the anaesthetic eyes. In Group 1 two patients had been injected on both sides, and three patients did not have Schirmer's test carried out; two of the three were unable to tolerate the filter paper in the control eye, and the third refused to have the test performed.

Table III shows that 37 per cent. of the control eyes gave readings of 5 mm. or less, and 40 per cent. gave readings of over 10 mm.

Table III *Schirmer's test in control eyes*

Group	*Schirmer's test results*										*Total readings*
	5 mm. or less		*6–10 mm.*		11–15 mm.		*16–20 mm.*		*over 20 mm.*		
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	
1	25	37	16	23	10	14	8	12	10	14	70
2	9	50	3	17	5	27	1	6	—	—	18

Table IV (overleaf) shows that 39 per cent. of anaesthetic eyes gave readings over 10 mm. and 15 per cent. over 15 mm.

Table IV *Schirmer's test in anaesthetic eyes*

Group	*Schirmer's test results*										*Total readings*
	5 mm. or less		*6–10 mm.*		*11–15 mm.*		*16–20 mm*		*over 20 mm.*		
	No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*	
1	27	39	15	22	17	24	8	11	3	4	70
2	8	44	6	33	3	17	1	6	—	—	18

Among the patients in Group 1 on whom Schirmer's test was carried out, seven anaesthetic eyes gave readings of zero, two being in a patient bilaterally Injected. Of the other five, in one the control eye also gave a reading of zero. The second patient in Group 1 who had been bilaterally Injected gave readings of 5 mm. and 9 mm.

Group 2 (20 eyes)

(*a*) *Visual acuity and examination of the cornea*

There was punctate epithelial keratitis in these eyes (Table V) but, as in Group 1, visual acuity was 6/12 or better; seven patients (35 per cent.) saw 6/6 or better, seven (35 per cent.) saw 6/9, and six (30 per cent.) saw 6/12. The patient with confluent coarse punctate keratitis had a visual acuity of 6/5 unaided, and in the other cases the visual acuity appeared to be unrelated to the amount of punctate staining present, so that as in Group 1 impairment of vision was not attributable to damage to the cornea. When the keratitis was partial it was always confined to the lower part of the cornea. One of the two patients with medium punctate staining had a small leash of blood vessels growing into the cornea at 6 o'clock, but this coincided with an ingrowing lash which unknown to the patient must have been abrading the cornea since the Injection 6 years previously (this patient was one of two with a small lateral tarsorrhaphy). Three patients in this group had a single small linear opacity in the stroma; the aetiology of this is uncertain, but it may have indicated previous keratitis. Neither of the two patients in this group with a tarsorrhaphy showed any stromal changes.

Table V *Distribution of punctate epithelial keratitis in eyes of patients in Group 2*

Punctate epithelial keratitis	*Partial (less than half)*	*Confluent*
Fine	12	1
Medium	2	2
Coarse	2	1

(*b*) *Tarsorrhaphy*

Two patients in Group 2 had lateral one-third tarsorrhaphies. This had been carried out in the first patient (female, 70) within a few weeks of Injection, performed 6 months previously. The second patient (female, 39) had been Injected 6 months ago, and tarsorrhaphy had been carried out 2 weeks later.

(*c*) *Symptoms*

As in Group 1 symptoms were few and non-specific and related to dysaesthesiae.

(*d*) *Schirmer's test*

Control Schirmer's readings were possible in only eighteen of this group, because one patient had been Injected bilaterally.

Table III shows that 50 per cent. of the control eyes gave readings less than 5 mm., 33 per cent. gave readings over 10 mm.

Table IV shows that 23 per cent. of the anaesthetic eyes gave readings over 10 mm., and 6 per cent. over 15 mm.

Of the twenty eyes in Group 2 on which Schirmer's test was carried out, four anaesthetic eyes gave readings of zero, and in two of these the reading from the control eye was also zero.

Group III (5 eyes)

(*a*) *Visual acuity and examination of the cornea*

In this group keratitis was present and the visual acuity was reduced to less than 6/12 because of corneal changes. Details of these patients are set out in Table VI, and other facts about them are described below.

Table VI *Details of five patients in Group 3*

Patient No.	*Sex*	*Age (yrs)*	*Time since injection*	*Visual acuity*	*Schirmer's test*		*Tarsorrhaphy*	*Cornea*	*Other Ocular Pathology*
					Control	*Anaesthetic*			
1	F	67	5 yrs	6/24	20	20	None	Medium punctate epithelial keratitis lower nasal quadrant	Trichiasis Bilateral epiphora
2	F	52	1 yr	6/18	8	6	Lateral 1/3 2 wks after injection	Coarse confluent punctate epithelial keratitis Vessels above and nasally	? Rosacea
3	F	70	5 yrs	6/36	—	—	Central 1/3 2 wks ago	Fine central punctate epithelial keratitis	—
4	F	66	5 yrs	6/18	5	5	Lateral 2/3 1 mth after Injection	Superficial vessels infero-nasally Central stromal nebula	Dacryocysto-rhinostomy + Epiphora
5	M	62	6 mths	Counting fingers	—	—	—	Severe neurotrophic keratitis	Uveitis

PATIENT 1

This woman aged 67 years complained of photophobia and she had bilateral epiphora. On the side of the Injection some lashes were abrading the cornea, for which she was attending her local eye hospital. There was punctate staining of the cornea, but her poor visual acuity may have been partly due to epiphora and photophobia. She was mentally not normal.

PATIENT 2

This woman aged 52 years had neurotrophic keratitis as well as pre-existing corneal scarring. The appearance of the cornea was consistent with rosacea keratitis, but there were no obvious cutaneous manifestations of this condition.

PATIENT 3

This woman aged 70 years, who had been Injected 5 years previously, had no eye problems until 9 months before the examination; her eye had then been injured by a hair spray and not long afterwards exposed to smoke from a bonfire. She had since suffered from intermittent redness of the eye, and a central one-third tarsorrhaphy had been carried out 2 weeks earlier at her local hospital.

PATIENT 4

This woman aged 66 showed no active keratitis, but there was central stromal scarring. She had undergone a dacryocystorhinostomy on the side of the Injection a year before the Injection, but the epiphora had not been cured. She admitted to wiping and rubbing her eye frequently, and when seen in the clinic was accompanied by a strong aroma of alcohol. In the notes there was a history of excessive alcohol intake. A tarsorrhaphy had been performed a month after the Injection 5 years previously.

PATIENT 5

This man aged 52 had been seen at routine follow-up 5 months previously (one month after Injection) when his visual acuity was recorded as 6/6. On this occasion his vision was reduced to "counting fingers"; he was found to have a severe neurotrophic keratitis with secondary uveitis and was referred for immediate tarsorrhaphy. He stated that his eye had been bloodshot for 1 week, after exposure to a high wind on a sandy beach. He had decided to do nothing about it as it would have interrupted his holiday; he was in fact a rather simple man.

It can be seen that in two of these patients in Group 3 (Patients 1 and 4) there was other ocular pathology in addition to an anaesthetic cornea, and in a third (Patient 2) there may have been unrelated corneal disease superimposed on neurotrophic changes.

(*b*) *Schirmer's test*

It was possible to carry out Schirmer's test on only three patients in this group. Patient 3 had a recently performed central one-third tarsorrhaphy which made an accurate Schirmer test impossible, and Patient 5 had a severe neurotrophic keratitis. Little information was therefore forthcoming from the Schirmer tests (Tables III and IV). The control side gave a wetter reading than the anaesthetic side in one patient, and in the other two the results from the two sides were the same.

These five patients were aware that their vision was blurred, and the acuity in each had deteriorated since the Injection.

Discussion

Magendie (1824) was the first to describe degenerative changes in the cornea after section of the trigeminal nerve in animals; since then much work has been carried out to determine the aetiology of these changes, and many hypotheses have been put forward. Paton (1926) and Rowbotham (1939), while both considering that analgesia of the cornea was the essential primary factor, thought that desiccation played an important role. This concept was supported by de Haas (1962), but he went on to say that, important though desiccation is, its primary cause must be sought in changes in the tissues themselves. The best known hypotheses were summarized by Duke-Elder and Leigh (1965), who concluded by saying that abnormal cellular metabolism seemed to provide the most adequate explanation of the phenomenon of neurotrophic keratitis. According to this theory, trophic disturbances are due to the lack of normal peripheral antidromic activity; the anaesthesia is incidental but facilitates trauma which the abnormal cornea is unable to repair in the normal way.

The incidence of neurotrophic keratitis in lesions of the trigeminal nerve varies according to the site of the interruption of the pathway. Paton (1926) considered that it developed more rapidly in ganglionic and infraganglionic lesions, but said that it undoubtedly occurred in supraganglionic lesions and those affecting the bulbo-spinal roots and their related nuclei. After suboccipital rhizotomy the incidence is considerably reduced, and it has rarely been reported after medullary tractotomy (Guidetti 1950); in the latter operation fibres conducting pain are severed, but light touch is preserved (Sjöqvist 1937). Harris (1940), discussing the end-results of alcohol injection of the trigeminal root, said that neurotrophic keratitis was formerly a serious complication but went on to describe methods of diminishing the risk of its occurrence (see below). Penman (1950), reviewing the results of 82 intracranial (root) injections causing anaesthetic corneae, referred to the high incidence of keratitis; he reported the incidence of keratitis requiring tarsorrhaphy as 18·3 per cent. Pannabecker (1944), reviewing 878 operations of various kinds for trigeminal neuralgia, reported an overall incidence of corneal lesions of 18 per cent., but was unable to draw any conclusions about sensory root injections since his series included only four of them. Subtotal rhizotomy involving the ophthalmic division and total rhizotomy produced an incidence of corneal lesions of 25 and 30 per cent. respectively. The incidence of corneal lesions following operations for trigeminal neuralgia which produced corneal anaesthesia (434 in all) was 29 per cent., the figure rising even higher if orbicularis paralysis was also present. Of these, 13 per cent. of the lesions were mild, and in 17 per cent. the condition was a severe form of neurotrophic keratitis. In an effort to indicate the relative seriousness of the various lesions, an attempt was made to record the final visual acuity. This had to be done by means of correspondence with the patients (only half of whom replied), and therefore the data obtained, which merely stated whether the patient had "reading vision", were not of great value. Pannabecker (1944) found that keratitis developed in only about 25 per cent. of cases within the first week after operation, but in 80 per cent. the onset was within 6 months.

For neurotrophic keratitis, prophylaxis is far better than treatment (Pannabecker, 1944; Stookey and Ransohoff, 1959; Penman, 1960). Harris (1940) reported that stellate ganglionectomy diminished the liability to keratitis, and that trophic ulceration healed readily. Baker and Gottlieb (1959) referred to evidence produced by Dott at the Harvey Cushing Society Meeting in 1955 in which he stated that, when the superior cervical ganglion was removed in patients with anaesthetic corneae after alcohol injection of the fifth nerve, not a single instance of corneal ulceration was noted in a fairly large series of patients. It is of interest that one of the patients in Group 1 (male, 61) had undergone cervical sympathectomy in an unsuccessful attempt to relieve his tic douloureux 17 years previously. Most surgeons agree that a pad and bandage is contraindicated. If the keratitis does not respond to conservative measures within a few days, tarsorrhaphy is the recommended treatment (Paton, 1926; Harris, 1940; Pannabecker, 1944; Stookey and Ransohoff, 1959; Penman, 1960). Harris (1940) found the risk of keratitis much diminished by the regular instillation of liquid paraffin drops four times a day, and many surgeons advocate a protective shield for the first few weeks of anaesthesia; protective side-pieces can be fitted to spectacle frames, and are more satisfactory because they do not move.

Analysis of results

Of the eyes examined, 75 per cent. had normal corneae with no evidence of any damage having been suffered as a result of corneal anaesthesia, nor was any visual impairment attributable to corneal damage. 20 per cent. of eyes showed evidence of neurotrophic keratitis but this was of mild degree in most cases and did not impair vision. In this group of patients slight stromal scarring was found in three cases only, and there was no evidence that it followed earlier neurotrophic keratitis. Patients in both these groups were unaware of any visual disturbance, and had no significant ocular symptoms. In the remaining 5 per cent. neurotrophic keratitis was severe enough to impair vision.

It can reasonably be assumed that some degree of trophic disturbance occurs in all anaesthetic corneae. The time and severity vary from case to case (*e.g.* the third patient in Group 3 who had no trouble for 5 years), but every patient runs the risk of developing neurotrophic keratitis at any time. The interest lies in trying to determine what factors may predispose to its development, and why in this series of 100 anaesthetic corneae only 5 per cent. should have developed serious trouble.

In the three groups there was no significant age difference between the patients, or in the length of time that had elapsed since the Injection. The great majority of patients were given the same precise and complete type-written instructions on care of the eye after Injection, with particular emphasis on the importance of not touching or rubbing the eye, or getting soap or other irritants in it. They were also instructed to test the vision in the eye each day, and to consult an ophthalmologist without delay if it was blurred for more than 24 hours. Occupation might be thought to be an important factor, but in this series there was no evidence that patients who worked out-of-doors or in a dusty atmosphere were more prone to develop keratitis. For instance, Group 1 included a paint-sprayer, a mattress-maker, a lathe worker in a metal workshop, an aircraft fitter, and a factory hand in a fibre-glass factory. Group 2 included two patients living in dry climates in Western Australia and Cyprus, each with only a small area of fine punctate keratitis and 6/6 visual acuity, and no ocular problems. All five patients in Group 3 lived an indoor life; all the females were housewives, and the fifth was retired.

If the patients in Group 1 are taken as the "control" group (as they all have normal corneae) there are certain differences between them and the patients in Group 2 in the results of the Schirmer tests.

From Table III, which shows the readings from the control eye, it can be seen that 50 per cent. of eyes in Group 2 gave readings of less than 5 mm. compared with 37 per cent. with similar readings in Group 1. In addition, whereas 40 per cent. of eyes in Group 1 gave readings over 10 mm., only 33 per cent. from Group 2 did so; moreover, no reading was greater than 20 mm. in comparison with 14 per cent. in Group 1 which gave readings over 20 mm.

From Table IV, which shows the readings from the anaesthetic eyes, it can be seen that 39 per cent. of the eyes in Group 1 were over 10 mm. compared with 23 per cent. in Group 2; moreover 15 per cent. were over 15 mm., but only 6 per cent. gave similar readings in Group 2.

Together these results suggest that reflex lacrimation of patients in Group 1 is greater than that of those in Group 2.

Other differences between the patients in this series may be seen by comparing the patients in Groups 1 and 2 (those with normal corneae or minor degrees of keratitis) with the patients in Group 3 (those with more severe corneal damage). Two points emerge: (1) In two, and perhaps three, patients in Group 3 there was other ocular pathology which undoubtedly had an adverse effect upon the anaesthetic corneae. (2) Of the five patients in Group 3 three could not be regarded as psychologically normal.

Conclusions

(1) Reduced reflex lacrimal secretion is a factor in some patients in the development of neurotrophic keratitis. It is suggested that a Schirmer test be carried out on patients who are to undergo operative treatment which may result in corneal anaesthesia. By this means it may be possible to forecast which patients are more likely to develop neurotrophic keratitis, and extra care can be taken to warn them of the signs and symptoms which may indicate that it is developing.

(2) Trichiasis, any suspicion of blockage of the tear ducts, and any inflammatory or other condition of the cornea, existing before surgery of the trigeminal nerve, may increase the risk of postoperative neurotrophic keratitis. These conditions should be investigated and treated before operation is undertaken.

(3) Patients with personality defect or mental inadequacy are more likely to develop neurotrophic keratitis than normal individuals; they should be selected with particular care for surgery, and their progress watched with special vigilance.

(4) Although keratitis usually occurs within a short time of operation, trauma may precipitate it years later; if this is reported and dealt with promptly no permanent damage will result.

Summary

One hundred anaesthetic corneae in 97 patients were examined after alcohol injection of the trigeminal ganglion. 75 per cent. of corneae were normal. 20 per cent. showed some evidence of neurotrophic keratitis but this was of small degree and insufficient to reduce visual acuity. The remaining 5 per cent. showed permanent corneal changes and impairment of visual acuity. Possible factors influencing the onset and progress of the keratitis were decreased reflex lacrimation and trauma to the cornea.

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Chelation in experimental *Pseudomonas* keratitis

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In contrast to its occasional occurrence during the first half of the 20th century (Joy, 1942), *Pseudomonas aeruginosa* to-day ranks as a common, if not the most common, cause of bacterial corneal ulcer in the United States of America. Even with prompt laboratory diagnosis and use of adequate and specific antimicrobial therapy, the rapidly destructive lesion caused by this bacterium frequently results in severe visual impairment and often in corneal perforation with its attending complications. Such perforation is often predictable, in the experience of the author, when a spreading colliquative necrosis of the cornea continues to occur following conversion of daily cultures from positive to negative.

It has been suggested that this rapid corneal destruction may be the result of an extremely potent bacterial proteolytic enzyme (Fisher and Allen, 1958a, b; Fisher, 1958). This has been described as being intracellularly synthesized by *Pseudomonas aeruginosa*, released and extracellularly activated by available calcium cations (Morihara, 1963). The ability to split certain synthetic hexapeptides in a highly specific manner, plus its apparent action on the corneal stroma which is largely collagen, suggests further that this metallo-enzyme is in fact a collagenase (Schoellmann and Fisher, 1966).

Apart from *Pseudomonas aeruginosa*, only three groups of microbial organisms have been shown to produce such an enzyme (MacLennan, Mandl, and Howes, 1953; Rippon, 1968a, 1968b) (Table I).

Table I *Microbial organisms producing collagenase*

(1) *Clostridium histolyticum*
(2) *Pseudomonas aeruginosa*
(3) *Streptomyces madurae* (Nocardia)
(4) *Trichophyton schoenleinii*

All such collagenases demonstrate certain common features (Table II, overleaf). Of these properties, the ability of low concentrations of the disodium salt of ethylenediamine tetra-acetic acid (Na_2EDTA) to inhibit enzymatic hydrolysis of the substrate collagen appeared to have some therapeutic possibilities in the management of *Pseudomonas* keratitis. It was the purpose of this investigation to determine experimentally whether this might be so.

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Table II *Characteristics of microbial collagenase*

Organism	*Ca^{+2} Metallo-enzyme*	*Inhibition Na$_2$EDTA*	*Inhibition cysteine*	*Enzyme disrupters*
Clostridium histolyticum	+	+ .. R	+ .. NR	Urea Heavy metals
Pseudomonas aeruginosa	+	+ .. R	+ .. NR	Urea Heavy metals KMnO$_4$
Streptomyces madurae	+	+ .. R	+ .. NR	Urea Heavy metals
Trichophyton schoenleinii	+	+ .. NR	+ .. NR	Urea Heavy metals

R = Reversible inhibition
NR = Nonreversible inhibition

Material and methods

Four strains of *Pseudomonas aeruginosa* isolated from clinical cases of keratitis were evaluated for their ability to produce proteolysis by inoculation onto a special protein* and gelatin medium. The same isolates were also inoculated onto this medium containing Na$_2$EDTA in concentrations of 2·5 × 10^{-3}M, 5 × 10^{-3}M, and 10^{-2}M respectively. Incubation was at 27°C. and the cultures were observed for evidence of proteolysis at 24, 36, and 48 hrs. This was determined in gelatin by liquefaction while on the opaque protein media by a clearing to near transparency extending outwards from the inoculation site.

Cell-free filtrates of the four strains grown for 36 hours in 5 per cent. peptone broth, both with and without 10^{-2}M, Na$_2$EDTA, were obtained using a Millipore (0·22u) filtration system. Collagen strips† were then incubated in these filtrates at 37°C. and observed at 24, 36, and 48 hrs for gross evidence of hydrolysis. No attempt was made to determine the amino acid content of the proteolytic end products.

Since, during the *in vitro* phase, all of the *Pseudomonas* strains behaved in an identical fashion, one was chosen at random to continue the study.

Using techniques previously described by earlier investigators (Morihara, 1963), a crude enzyme extract was obtained from cell-free filtrates of this strain grown for 36 hrs in a 5 per cent. peptone broth. The enzyme was reconstituted with phosphate buffer (pH 7·2) and 1/10 of a millilitre injected intrastromally in the right cornea of six adult albino rabbits. The enzyme extract was also reconstituted in 10^{-2}M Na$_2$EDTA buffered to pH 7·0, and an identical amount was injected similarly into the left cornea of the same animals. They were then observed at 12 and 24 hrs for evidence of liquefactive corneal necrosis.

To ascertain the effect of Na$_2$EDTA in the face of actual infection, both corneae of 24 adult albino rabbits were inoculated with overnight cultures of *Pseudomonas aeruginosa* grown in tryptic soy broth, using the Hessburg technique of running a contaminated 6–0 black silk suture through the superficial stroma (Hessburg, Truant, and Penn, 1963). Between 18 and 20 hrs after inoculation, the animals were divided into two groups of twelve each for treatment. In all of the 24 animals, both eyes were treated with a gentamicin-carbanicillin mixture (8 mg. gentamicin-4 mg. carbanicillin per ml.) in 1 per cent. methylcellulose, administered hourly from 8 a.m. to 8 p.m. for 7 days, then four times daily for another week. In one group of twelve animals, the left eye was additionally treated with a 10^{-2}M solution of Na$_2$EDTA in 1 per cent. methylcellulose (pH 7·0) four times daily for 2 weeks; in the other group of twelve a 0·5 per cent. Na$_2$EDTA ointment was applied to the left cornea four times daily for the same period of time. In all animals both corneae were cultured for *Pseudomonas* before starting treatment and in the morning daily thereafter for 14 days. All corneae were observed daily for progress of the infection as manifested by corneal infiltration, extent of liquefactive necrosis (softening and/or loss of stroma), descemetocoele, or perforation (Tables III and IV for grading).

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*Protein medium 0·2 per cent. casein, 0·3 per cent. beef extract, 0·5 per cent. tryptone, 0·1 per cent. glucose, and 1·5 per cent. agar (pH 6·7).

†Collagen strips 3 × 2 mm. strips of rabbit achilles tendon aseptically obtained and bacteriologically sterile.

Table III *Evaluation Day 7 Na_2EDTA $10^{-2}M$ in 1 per cent. methylcellulose*

Rabbit no.	*Antibiotics only Right eye*	*Antibiotic + Na_2EDTA $10^{-2}M$ Left eye*
1	4	2
2	4	2
3	3	1
4	4	3
5	3	2
6	3	2
7	4	2
8	3	1
9	3	3
10	4	2
11	4	2
12	4	2
Average	3·58	2·00

Table IV *Evaluation Day 7 Na_2EDTA 0·5 per cent. Ointment*

Rabbit no.	*Antibiotics only (Right eye)*	*Antibiotic + 0·5 per cent. EDTA ointment (Left eye)*
1	4	3
2	3	2
3	3	2
4	4	2
5	4	2
6	4	1
7	3	2
8	4	2
9	4	1
10	3	3
11	4	2
12	4	2
Average	3·66	2·00

Grade 0 No ulceration, 0 mm.
Grade 1 Central infiltration, superficial necrosis 1–3 mm.
Grade 2 Central infiltration, superficial necrosis 3–5 mm.
Grade 3 More than one-half cornea infiltrated, extensive necrosis, loss of stroma, descemetocoele
Grade 4 Entire cornea infiltrated, extensive necrosis, loss of stroma, perforated

Results

During the *in vitro* phase all strains behaved in an identical fashion, causing a rapid enzymatic clearing of the opaque protein media and liquefaction of the gelatin within 24 hrs. At a concentration of $2{\cdot}5 \times 10^{-3}$M, Na_2EDTA had no sustained inhibitory effect on proteolysis, either on the protein media or on gelatin, and at 5×10^{-3}M Na_2EDTA, there was inhibition of gelatin liquefaction, but proteolysis was noted at 48 hrs on the opaque protein media. The media incorporating 10^{-2}M Na_2EDTA exhibited no evidence of proteolysis even at the end of a week. The addition of sterile 10^{-3}M calcium chloride at this time resulted in the appearance of proteolytic activity within 24 hrs.

In the cell-free filtrates with no Na_2EDTA, hydrolysis of the collagen strips was partial at 24 hrs and complete in from 36 to 48 hrs. However, on incubation with the filtrates containing 10^{-2}M Na_2EDTA, there was no apparent enzymatic digestion of the strips at the end of 48 hrs. As with the solid media, proteolytic activity was noted within 24 hrs after the addition of calcium chloride.

On intrastromal injection of 1/10 ml. of enzyme extract into the right cornea of six rabbits, there occurred a marked colliquative necrosis within 12 hrs in each animal. Apart from the absence of a mucopurulent conjunctival discharge, this looked quite like a *Pseudomonas* infection, although cultures were negative (Fig. 1A). The addition of 10^{-2}M Na_2EDTA to the enzyme preparation before intrastromal injection into the left cornea of the same six animals did not prevent a stromal reaction as manifested by central infiltration and superficial ulceration, but there was evident inhibition of the extensive liquifying necrosis noted in the right cornea (Fig. 1B).

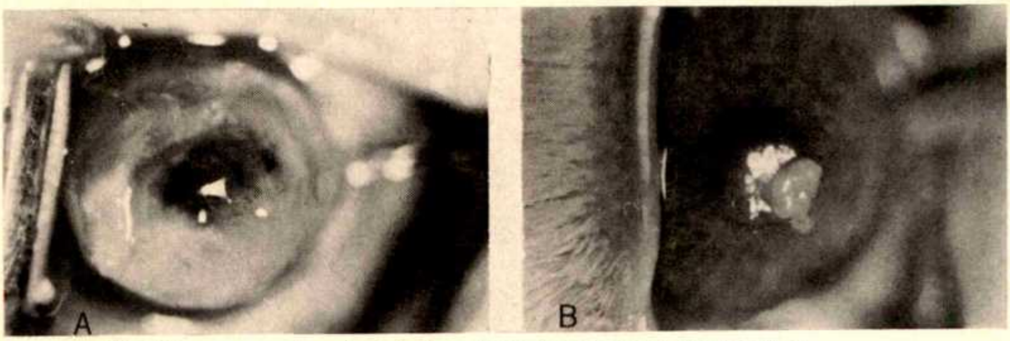

FIG. 1 (A) *Right cornea* 12 *hrs after intrastromal injection of* 0·1 *ml. enzyme extract.*

(B) *Left cornea of same animal* 12 *hrs after intrastromal injection of enzyme in* $10^{-2}M$ *Na_2EDTA*

All of the 24 animals inoculated exhibited evidence of bilateral corneal infection between the 18th and 20th hour after inoculation (Fig. 2A and B) and at this time, the particular form of therapy was initiated. In the right cornea of both groups treated with antibiotics alone, a liquefactive necrosis was noted to begin between the 22nd and 24th hour which progressed concentrically and in depth from the point of inoculation to involve most or all

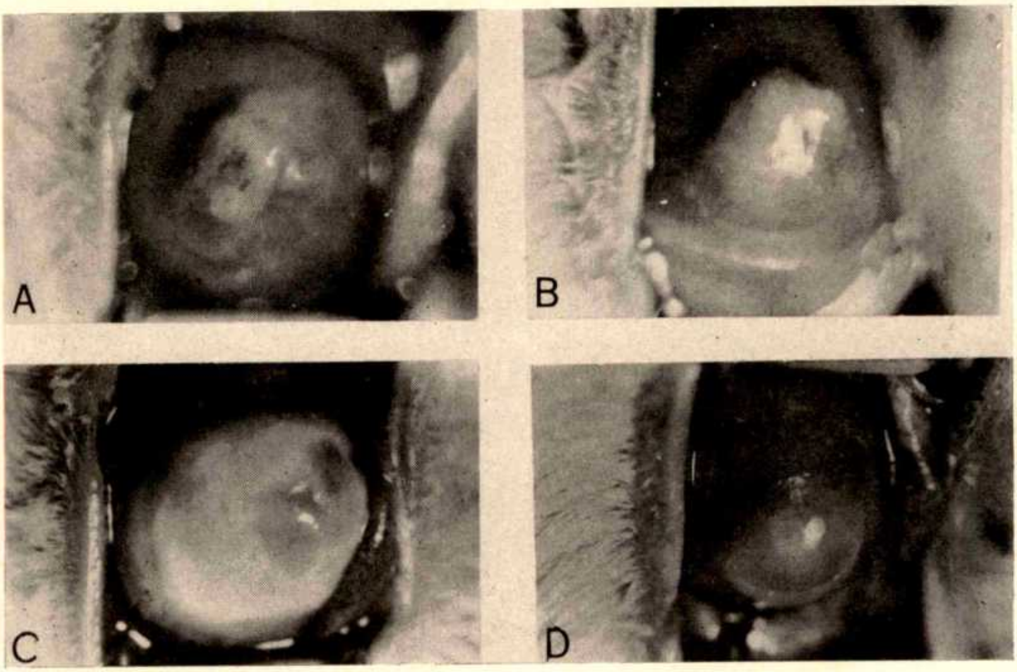

FIG. 2 *Representative animal.*

(A) Right eye 20 hrs after inoculation

(B) Left eye 20 hrs after inoculation

(C) Right eye on Day 7 treated with antibiotics only

(D) Left eye on Day 7 treated with antibiotics plus $10^{-2}M$ Na_2EDTA in 1 per cent. methylcellulose of the cornea, reducing its consistency from firm to gel-like. By the seventh day, fifteen right corneae from the total of 24 had perforated (Tables III and IV, Fig. 2C). This occurred in the face of specific antibiotic therapy and in spite of the fact that by the third day of treatment, all cultures from these eyes were negative for *Pseudomonas*.

In the left cornea of the twelve rabbits in group one treated additionally with 10^{-2}M Na$_2$EDTA drops four times daily, the results were somewhat different. By the fourth day there was ulceration at the site of inoculation and a spreading concentric infiltration of 5 mm. or more in most of the animals. However, in only two did a gel-like consistency develop and this was limited in comparison to the extensive destruction noted in the fellow right eye. The appearance of a descemetocoele was not noted in any of these left corneae by Day 7. As with the right eye, negative cultures were obtained by the third day of treatment (Table III, Fig. 2D).

In the second group of twelve rabbits, the left cornea was treated with 0·5 per cent. Na$_2$EDTA ointment four times daily in addition to the antibiotic drops. The results in these animals were much the same as in those eyes treated with Na$_2$EDTA drops. In no instance was perforation noted and ten of the twelve corneae maintained a firm stromal consistency (Table IV).

In all animals, the second 7 days of therapy on both sides appeared to be periods of resolution from the initial insult. In the 24 right corneae there was dense scarring, extensive neovascularization, and in those which perforated adherent leucoma formation. On the left side neovascularization, although present, was less; and while there was central scarring, the peripheral cornea seemed to clear somewhat. At the end of one month, the difference between the two sides was quite apparent (Fig. 3).

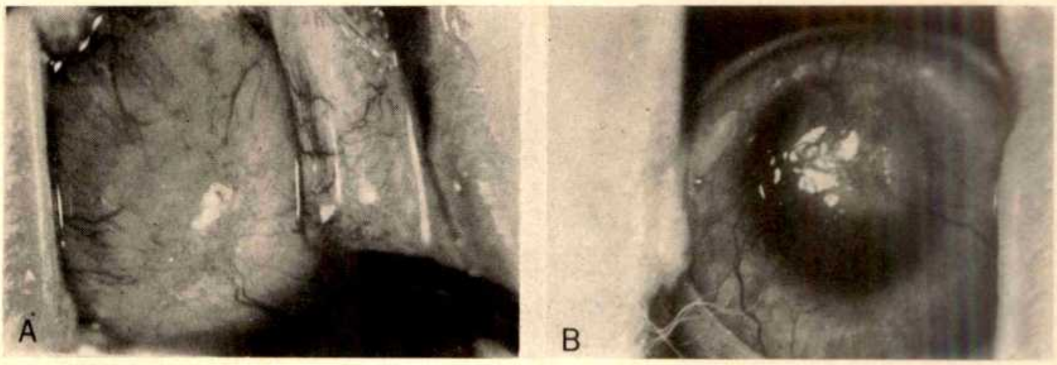

FIG. 3 *Representative animal 1 month after inoculation*

(A) Right eye treated with antibiotics only

(B) Left eye treated with antibiotics and 10^{-2}M Na$_2$EDTA

Discussion

From the results of this study plus his clinical experience, the author concurs with the observation of Hessburg and others (1963) that both in experimental and in most clinical instances of *Pseudomonas aeruginosa* keratitis, the majority of evident damage is accomplished by the fourth day of active disease. The continuation of this damage in the face of negative cultures would suggest that it is caused by more than the simple presence of replicating bacteria.

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Although in this series of experimental infections only one strain of *Pseudomonas aeruginosa* was used, studies in this laboratory have since shown that, when any of our clinical cornea isolates are inoculated into the rabbit cornea and treated with antibiotics alone, the results are almost identical.

Several years ago Fisher (1958) and Fisher and Allen (1958a, b) suggested that a *Pseudomonas*-elaborated proteolytic enzyme may be the cause of major damage in such corneal infections. Since then, Morihara and Tsuzuki (1964) have shown that *Pseudomonas aeruginosa* does indeed produce such an enzyme, a peptidohydrolase. They have also demonstrated that it is a calcium activated metallo-enzyme. More recent studies have indicated that this enzyme may be a collagenase akin to that produced by *Clostridium histolyticum* (Schoellmann and Fisher, 1966).

This investigation accepts the results of these earlier studies, and no effort was made to duplicate them or prove that this enzyme is specifically a collagenase. However, its results confirm the proteolytic effect of *Pseudomonas aeruginosa* on various media and collagen strips. That Na_2EDTA can block such action without interfering with bacterial growth and that such inhibition is reversible on the addition of dilute calcium chloride solution lends support to the concept that this enzyme is calcium dependent. The ability of a crude extract of this enzyme when injected intrastromally to mimic an infection in the absence of bacteria suggests further that it is this bacterial product which is primarily responsible for the extensive corneal destruction seen in *Pseudomonas aeruginosa* keratitis.

The concept of employing a chelating agent *in vivo* to block the destructive effect of bacterial enzyme systems is not a new one. Lynch and Moskowitz (1968) have reported on the ability of various chelators administered parenterally to protect animals against otherwise lethal doses of *Clostridium perfrigens* alpha toxin, a lecithinase. This enzyme, considered to be the lethal factor in gas gangrene, is apparently a zinc metallo-enzyme.

In instances of *Pseudomonas* keratitis, it seemed that, if one could inhibit the action of the bacterial protease while concurrently administering antibiotics to eliminate the enzyme source, the therapeutic outcome might be somewhat better than is currently the case. On the basis of these initial results it would appear that this may be possible. The protection afforded by EDTA may possibly be two-fold. Similar to its effect in various protein media, it can chelate available free calcium cations (as noted in Fig. 4, Reaction 1), making them unavailable for enzyme activation. The unactivated enzyme may then bind to stromal lamellae (Fig. 4, Reaction 2) but, unactivated by calcium, no proteolysis occurs. It may also undergo autodigestion. As an additional protective measure it is quite probable that Na_2EDTA forms a calcium chelate-enzyme complex with the already activated enzyme (Fig. 4, Reaction 4) and thus makes it unavailable for proteolysis (Morihara and Tsuzuki, 1964).

The kinetics of enzyme-substrate interaction and constant replenishment of calcium from tears, cornea, and aqueous, would dictate that, in the living cornea, complete inhibition of stromal digestion in the presence of infection and enzyme production is not possible. This may explain the modified necrosis noted in the left Na_2EDTA-treated corneae of both groups of animals.

There are other methods of inhibiting this proteolytic activity. However, our experience with enzyme disruptors such as 6M urea and heavy metals have not met with much success, their application to the cornea frequently being as destructive as the infection itself, or more so. Cysteine would appear to possess some therapeutic potential, but so far our results *in vivo* have not been as productive as with Na_2EDTA. The N-acetyl derivative of cysteine, available commercially as a mucolytic agent, had no effect at all. We are now

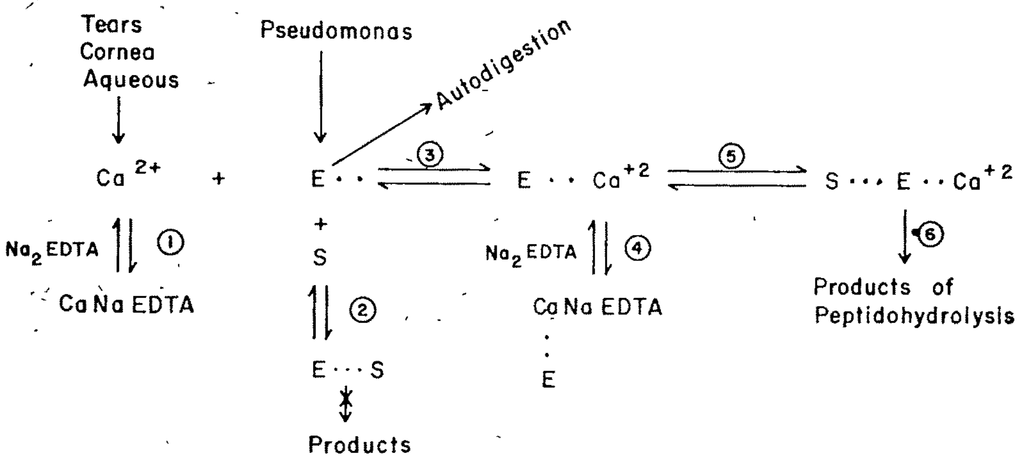

FIG. 4 *Schematic representation of possible action of Na$_2$EDTA in inhibiting enzymatic hydrolysis of stromal collagen*

investigating the use of more effective polycarboxylic amino acids as calcium chelators in an effort to inhibit this colliquative stromal necrosis in *Pseudomonas* keratitis, and experimentally at least several appear quite promising.

Summary

Clinical isolates from pseudomonal infections of the human cornea were evaluated for their ability to produce proteolysis, both *in vitro* and *in vivo*. A crude enzyme preparation was obtained from cell-free filtrates of *Pseudomonas aeruginosa* grown for 36 hrs in a 5 per cent. peptone broth. When a minute amount of this enzyme was injected into the corneal stroma of the experimental animal, a necrosis mimicking a clinical infection was noted to occur within 12 hrs. This necrosis was inhibited to a considerable degree by the addition of 10^{-2}M disodium EDTA. Similarly experimental infections in the rabbit cornea, when treated with appropriate antibiotics and a topical application of disodium EDTA, were noted to resist the extensive colliquative necrosis seen in similar corneae treated with antibiotics only.

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Failure of filtration operations in the African

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Filtration operations in Negroes and in other heavily-pigmented races have earned a bad reputation for a high rate of failure, but it is difficult to estimate the extent of this failure because it is difficult if not impossible to achieve an adequate follow-up in these cases (McNair, 1951; Welsh, 1969). Iliff (1944) reported a success rate of 23 per cent. with trephine operations and of 50 per cent. with iridencleisis. Berson, Zauberman, Landau, and Blumenthal (1969), in a series of 119 African patients, found a success rate of 39 per cent. for trephines, 26 per cent. for Scheie procedures, and 4 per cent. for iridencleisis. Our success rate is also roughly 30 to 50 per cent. (trephine and Scheie operations). In white patients on the other hand, Friedenwald (1950) reported a success rate of 80 to 90 per cent. and Scheie (1962) of more than 90 per cent.

The special problems encountered in Negroes and other dark-skinned patients have been attributed to a tendency to develop scar tissue more easily. Friedenwald (1950) stated that a study of eyes enucleated after drainage failures showed more episcleral scarring in the eyes of Negroes than in those of white patients. Luntz and Smith (1960) found pathological episcleral fibrosis to be present in four Negro patients undergoing drainage operations and postulated this as a cause of the glaucoma and thus of the low rate of success. McNair (1951) sent out a questionnaire to 125 ophthalmologists in the United States of America concerning chronic simple glaucoma in the Negro. He concluded that failure of fistulization was due to cicatrization of the bleb which was related to a thick Tenon's capsule which flayed out early. He also mentioned the thicker iris which impinged on the angle and the high percentage of positive Wassermann reactions (29·8 per cent.) with an increased tendency to form inflammatory exudates. The tendency to keloid formation causing fibrosis and adherence of conjunctiva and Tenon's capsule to sclera is generally accepted (Scheie, 1969).

The purpose of this paper is to review those of our filtration operations that failed in order to provide useful practical information on a problem which is no longer a surgical curiosity. Our cases show, on gonioscopic evidence and in a number of re-operations, that the failure of fistulization was due to a localized overgrowth of the external fistulous opening by fibrous tissue coming either from the walls of the scleral opening or from Tenon's capsule. This occurs soon after the operation with no bleb formation and anterior synechiae, though present, are of significance in only a few cases. There is no abnormal episcleral fibrosis preoperatively in the majority of cases and Tenon's capsule is not thickened. Since blebs do not form, the problem of cicatrization of a non-draining bleb did not arise.

Positive Wassermann reactions were only found in 5 per cent. of all the African patients attending the hospital, and do not appear to affect the postoperative results.

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Material and methods

During a 24-month period (October 1, 1967, to September 30, 1969), 143 drainage operations were performed on cases of chronic open-angle glaucoma in African and Indian patients; 103 of them were lost to follow-up, either because the patient did not return or because the records were not available, so that a correct estimate of success and failure rates is not possible. Of the forty cases which were followed, 28 (29 eyes) showed a sustained increase in intraocular pressure despite medical treatment, and these cases form the subject of this paper.

Of these 28 patients, 27 were Africans (Zulu tribe) and one was an Indian. There were fifteen males and thirteen females, and their ages ranged from 21 to 76 years.

The patients were examined particularly for the appearance of the drainage bleb; the gonioscopic appearance of the angle; the presence of synechiae; and the site of the internal opening of the scleral fistula.

The appearance of the external opening of the scleral fistula with or without conjunctival fibrosis was examined in cases in which re-operation was undertaken.

Conjunctival fibrosis was judged to be present if the conjunctiva was adherent to the scleral opening or was obviously blocking it. If the conjunctiva could be separated from the sclera and the scleral opening with ease, no pathological conjunctival fibrosis was judged to be present. The external scleral opening was either patent or so badly blocked by tissue derived from the surrounding sclera or from Tenon's capsule that one had to search for the position of the peripheral iridectomy in order to find the site of the previous drainage channel.

Results

Table I shows the operations that were originally performed and the number of eyes that had anterior synechiae. The most significant feature was that only one eye showed a drainage bleb.

Table I *Eyes with anterior synechiae and drainage blebs*

Original operation	*No. of eyes*	*Anterior synechiae*	*Bleb*
Trephine	15	12	1
Scheie	12	10	–
Post-sclerectomy	2	1	–

Table II shows the gonioscopic findings in seventeen eyes which had originally undergone drainage operations that had proved unsuccessful. There were no drainage blebs present. Anterior synechiae were present at the drainage site in fifteen eyes, but were judged to be sufficiently extensive to contribute towards blockage only in five. Scleral tissue blocking the drainage fistula on its inner aspect could be seen in five eyes.

Table II *Site of obstruction in seventeen cases of drainage failure not undergoing re-operation*

Original operation	*No. of eyes*	*Severe anterior synechiae*	*Bleb*	*Internal scleral overgrowth*	*External scleral obstruction*
Trephine	7	3	–	3	1
Scheie	8	2	–	2	4
Post-sclerectomy	2	–	–	–	2

Table III shows the gonioscopic and operative findings in the twelve eyes that underwent a second drainage operation. Anterior synechiae were present in eight, but were considered significant in only one. One eye developed malignant glaucoma with its attendant complications. The remaining ten eyes all showed blocking of the drainage fistula in the scleral portion, by scleral tissue or by fibrous tissue. It was difficult to assess the origin of this fibrosis but it probably derived from Tenon's capsule. Scleral tissue has little tendency to fibroblastic activity (Maumenee, 1967) and the surface of the external scleral opening was so effectively closed that in some cases it was difficult to find the site of the original scleral fistula. Three of the eyes showed conjunctival fibrosis as well as scleral fibrosis and in one eye the conjunctival fibrosis was marked. However, conjunctival fibrosis causing blockage was not as significant as one would have expected. In eight eyes, the conjunctiva was reflected away from the sclera easily enough, and the drainage fistula was found to be completely overgrown by tissue flush with the sclera. Two of these eyes had shown internal scleral overgrowth gonioscopically, and the scleral canal was occluded by fibrous tissue from its walls.

Table III *Site of obstruction in twelve eyes undergoing re-operation*

Original operation	*No. of eyes*	*Severe anterior synechiae*	*Bleb*	*Internal scleral overgrowth*	*External obstruction*	
					Scleral	*Conjunctival*
Trephine	7	–	–	2	6	2
Scheie	5*	1	–	–	2	1

*One case of Scheie procedure developed malignant glaucoma

Table IV shows three cases in which drainage operations had been performed on both eyes, but had been unsuccessful in only one. This gave a unique opportunity to compare the gonioscopic appearances in the two eyes. In each eye that was successful, a drainage bleb was present and in the eyes that had failed there was no bleb. All eyes showed anterior synechiae and the drainage fistula had been placed anterior to the canal of Schlemm. In the first case, the internal opening of the drainage fistula looked closed, yet the drainage was successful, and in the other eye, in which the internal opening appeared to be wide open, there was no drainage. Gonioscopic appearances are therefore deceptive, but these cases illustrate that the block in drainage is on the external side of the scleral canal.

Table IV *Gonioscopic appearances in three cases of bilateral operation with unilateral failure*

Original operation	*Eye*	*Date of original operation*	*Present tension (mm. Hg)*	*Bleb*	*Anterior synechiae*	*Probable site of block*
Scheie	R	16.4.68	18	+	+	—
	L	1.4.68	26	–	+	External scleral opening
Trephine	R	17.3.69	11	+	+	—
	L	6.6.69	35	–	+	External scleral opening
Scheie	R	9.8.67	20	+	+	—
	L	25.8.67	30	–	+	External scleral opening

Discussion

Failure of filtration operations has been adequately dealt with in the past. Maumenee (1967) showed that the causes were intraocular (due to lens, iris, or vitreous); scleral (narrow drainage cleft or persistence of Descemet's membrane); and extraocular (trauma, haemorrhage, inflammation to flap, foreign material under flap). We have found that all these causes occur in our patients but in the African particularly, the iris, sclera, Tenon's capsule, and conjunctiva react more severely to surgical trauma. What therefore are the differences between the Negro or African and the Caucasian eye? Boles-Carenini, Buten, Spurgeon, and Ascher (1955) found physiologically that there are no differences. They studied the normotensive eyes of 107 white and 97 Negro persons and found that the dynamics of the aqueous humour were equal in both groups and that the intraocular pressure, facility of aqueous outflow, and production of aqueous were also the same. Anatomically, the brown iris in pigmented eyes does not dilate readily and the trabecular tissue shows more pigment on gonioscopic examination. The heavily-pigmented iris shows a tendency to postoperative iritis and adhesions. Considering iris behaviour first, 80 per cent. of our cases showed anterior synechiae. Allen (1966) found anterior synechiae in only four of 34 postoperative drainage cases presumably in whites. Sollom (1969) found that 45 out of 54 cases of Scheie procedures showed anterior synechiae. These have been proved to be unimportant and Sollom found only four cases with a raised intraocular pressure. He related anterior synechiae formation to preoperative anterior chamber depth. In Table IV all three cases showed anterior synechiae whether there was successful drainage or not. Nevertheless, since postoperative iritis and flat anterior chamber are common in our cases, the easily-formed and prominent anterior synechiae may diminish aqueous flow through the scleral fistula, thus affecting bleb formation. Considering then the extraocular factors that lead to failure of drainage, the scleral reaction and Tenon's capsule reaction are much more evident than in white patients. However, at operation, when the conjunctival flap is reflected, we have noted any obvious episcleral fibrosis, and this was found in only one eye in the last forty glaucoma operations. In the other eyes, it was apparent that, even with a long-standing ocular tension of 60 mm. Hg, the conjunctiva was thin and easily reflected with little Tenon's capsule present. Therefore preoperative abnormal episcleral fibrosis can be discounted in most of our glaucoma patients. In addition, the drainage failures occur in the older age groups (over 50 years), since our patients present in the final stages of glaucoma and Tenon's capsule is thin. Then, when drainage fails, it does so early so that a bleb fails to form. Cicatrization of formed blebs with consequent nonabsorption of aqueous is not the problem that we have to deal with. The state of the conjunctiva is also noted during surgery, and again it is usually thin and appears to be normal. At the subsequent operation, the conjunctiva is no more adherent than one would find in Caucasian eyes, but the obstruction appears to come from Tenon's capsule at the scleral edges themselves, since the external fistula has been occluded by fibrous tissue overgrowth. Thus, although Tenon's capsule looks normal, it probably reacts excessively to trauma by providing fibroblasts for the cut scleral edges. Therefore, foreign substances placed subconjunctivally will not maintain long-term filtration unless the scleral canal is kept open. There is some doubt why fistulizing operations should work. DeVoe (1951) felt that it was due to trauma of the uveal tract and to readjustment of the neurovascular system. If the trabecular meshwork is opened up by the fistula, aqueous can pass through the side walls into the canal of Schlemm (Cairns, 1969). Teng, Chi, and Katzin (1959) suggested that aqueous had a deleterious effect on collagen and worked to prevent fibroblasts forming collagen. Thus the aqueous causes perivascular degeneration by affecting collagen around the blood vessels, and endothelial proliferation then occurs forming drainage channels. It is thus possible that in our African patients failure of drainage is due not to keloid formation but to a failure of aqueous to affect the fibroblasts and collagen tissue. With anterior synechiae formation, insufficient aqueous passes subconjunctivally and its effect is further reduced. Therefore physical methods of impeding fibroblast formation may prove helpful, and the best of these are beta irradiation (Simmons, 1959) and cryothermy to the sclera. In view of these findings, when a drainage operation is performed on an African patient, we attempt to improve the prognosis by the following measures:

The fistula should be made through the trabecular area. No cautery is used, since surface diathermy may cause conjunctiva to adhere to sclera. Deep diathermy will damage the canal of Schlemm through the side of the fistula. A large peripheral iridectomy is performed and surface cryothermy is applied to the sclera surrounding the fistula. Subconjunctival cortisone is injected to control postoperative uveitis.

It may be questioned, however, whether fistula operations with their attendant complications are indicated in African patients, and it was therefore decided to carry out internal trabeculectomy procedures (Cairns, 1968). Forty such operations have so far been performed with a certain amount of success, and the results will be available shortly.

Summary

Gonioscopic studies of 29 eyes in patients of the heavily-pigmented races (and in twelve of these confirmation at operation) have shown that failure of fistulization is due mainly to overgrowth of the external scleral fistula by fibrous tissue derived from the sclera and Tenon's capsule. Anterior synechiae are present in 80 per cent. of cases, filtration blebs do not form, and there is no preoperative abnormality in the episcleral tissues or in Tenon's capsule. Compared with Caucasian eyes, the reaction in Negro or Indian eyes to surgical trauma is more severe. The measures taken to overcome these problems include the use of a large peripheral iridectomy, cryothermy to the bare sclera surrounding the fistula, and subconjunctival cortisone.

I wish to thank Prof. L. Baker, Head of the Department of Surgery, and Dr. H. Wannenburg, Superintendent of King Edward VIII Hospital, for permission to publish these cases.

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Effect of moderate exercise on the ocular tension

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A few studies on the effects of hard or prolonged exercise on the ocular tension have reported a fall, except for the immediate rise which occurs on contraction of the abdominal and thoracic muscles (Comberg and Stoewer, 1925) or on the performance of the Valsalva manoeuvre (Biró and Botár, 1962). Short (100 m.) and middle distance (1,000 m.) running was associated with a fall, greater with the longer distance (Biró and Botár, 1962). However, after a 50 km. route march by 142 soldiers, 65·2 per cent. showed a rise, 15·7 per cent. a fall, and 19·1 per cent. no change (Kern, 1964). After severe exercise to exhaustion, Lempert, Cooper, Culver, and Tredici (1967) found a consistent fall in ocular tension.

In the present investigation, the effects on the ocular tension of walking (a more moderate type of exercise than those mentioned above) and sitting are compared.

Subjects and method

Fourteen healthy young adults, 12 males and 2 females, aged 21 to 35 years, were treated on two consecutive mornings in the following way:

(1) "EXERCISE" MORNING

- (*a*) Applanation tensions recorded from both eyes.
  Subjects sat in a library for 50 minutes.
- (*b*) Applanation tensions repeated.
  Subjects walked briskly for 50 minutes.
- (*c*) Applanation tensions repeated immediately after end of exercise.

(2) "RESTING" MORNING

- (*a*) Applanation tensions recorded from both eyes.
  Subjects sat in a library for 50 minutes.
- (*b*) Applanation tensions repeated.
  Subjects sat in a library for a further 50 minutes.
- (*c*) Applanation tensions repeated.

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In seven of the fourteen subjects the blood pressure was measured from the brachial artery (right arm in every case), using a sphygmomanometer cuff immediately after each applanation tension, (*a*), (*b*), and (*c*) above, had been recorded on each morning of the investigation.

The order in which subjects were exercised or rested was randomized so that, of the fourteen subjects, seven exercised on day (1) and rested on day (2) and seven rested on day (1) and exercised on day (2).

Each phase of the investigation was carried out at the same time of the day on exercise and resting days. A technician recorded the ocular tensions using a Goldmann applanation tonometer. The

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tension was always measured first from the right eye and then from the left. The measurements of the blood pressure were made by one of us (DAL).

Results

Changes in ocular tension which occurred after walking and sitting are recorded in Table I as differences between the second (*b*) and third (*c*) applanation readings, that is immediately before and after walking on the exercise day, and immediately before and after sitting in the library for the second period on the resting day.

Table I *Effect of walking compared with sitting on the ocular tension in fourteen subjects*

Subject no.	*Change in applanation tension (mm. Hg)*					
	Right eyes			*Left eyes*		
	* *Walking*	† *Sitting*	* *Net change (Walking-Sitting)*	* *Walking*	† *Sitting*	* *Net change (Walking-Sitting)*
1	−1	+1	−2	−1	−1	−2
2	−4	0	−4	−3	−1	−2
3	−1	−2	+1	−2	−2	0
4	−2	−2	0	−3	0	−3
5	−8	−3	−5	−5	0	−5
6	−2	+3	−5	−4	+2	−6
7	−2	+3	−5	−3	+4	−7
8	−1	+1	−2	0	+1	−1
9	−3	+1	−4	−1	−1	0
10	−3	−1	−2	−2	−2	0
11	+1	0	+1	0	+1	−1
12	0	−1	+1	0	+1	−1
13	−1	−2	+1	−2	−2	0
14	−5	−1	−4	−3	0	−3

Numbers in columns headed "walking" and "sitting" for right and left eyes refer to differences between applanation tensions recorded immediately before (*b*) and after (*c*) walking and sitting. A minus sign denotes a fall and a plus sign a rise. "Net Change" refers to the difference between the change after walking and that after sitting. A minus sign, for example, indicates that a fall after walking had been greater than a fall after sitting, and a plus sign, for example, that a fall after sitting had been greater than a rise after walking

* significant fall found in ocular tension when Wilcoxon test was used ($P < 0\cdot01$) in each case

† no significant change found in ocular tension

(*i*) *Effect of walking and sitting on ocular tension*

The Wilcoxon Matched Pairs Signed Ranks test (Siegel, 1956) was used to analyse these changes in ocular tension. The fall which occurred after walking was found to be statistically significant ($P < 0\cdot01$) for both eyes, but no significant change in ocular tension occurred after sitting.

(*ii*) *Net change in ocular tension due to walking* (*i.e.* subtracting "sitting" change used as control)

If the change in tension after sitting be regarded as the underlying trend of ocular tension during that period in the morning (*i.e.* the change after sitting being in the nature of a control) on which the change produced by walking is superimposed, then a "net" change (*i.e.* walking change *minus* sitting change) should be considered. The Wilcoxon test showed that there had been a significant fall (P < 0·01) in both eyes for walking compared with sitting.

The mean applanation tensions immediately before and after walking and sitting (readings (*b*) and (*c*) for right and left eyes) and the mean changes in tension corresponding to these are seen in Table II, and as bar charts in Fig. 1. Student's "t" test was used to

Table II *Mean applanation tensions (mm. Hg) in fourteen subjects immediately before and after walking and sitting, and the differences between them*

Eyes	*Right*				*Left*			
Reading	*Initial*	*Final*	*Difference*	*P*	*Initial*	*Final*	*Difference*	*P*
Walking	14·07	11·79	(fall) 2·28	<0·01*	13·64	11·57	(fall) 2·07	<0·01*
Sitting	14·14	14·00	(fall) 0·14	>0·05†	13·07	13·21	(rise) 0·14	>0·05†
Difference (Walking − Sitting)	0·07	2·21	2·14	<0·01*	0·57	1·64	2·21	<0·01*

* Significant at a level of less than 1 per cent.

† Not significant at a level of more than 5 per cent. (Student's "t" test was used to estimate P)

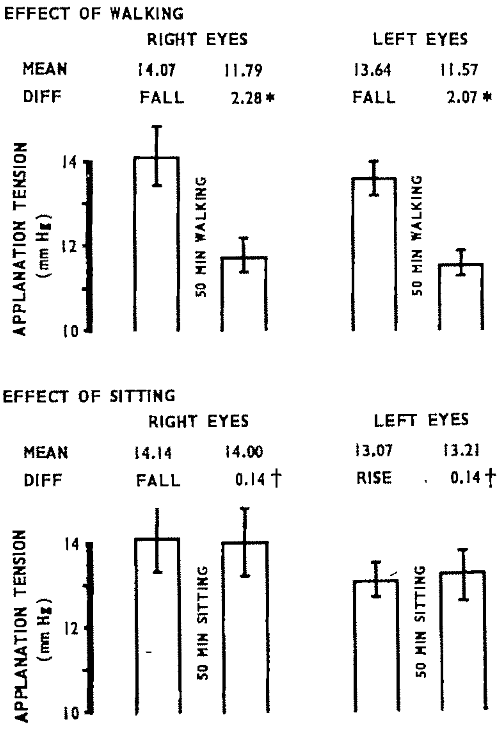

FIG. 1 *Bar charts, showing mean applanation tensions (mm. Hg) in fourteen subjects immediately before and after:*

ABOVE 50 *minutes walking*
BELOW 50 *minutes sitting*

The standard error of the mean is indicated on each bar

*Significant at P < 0·01 using both the Wilcoxon test and Student's "t" test

†Not significant by either of these tests.

estimate the significance of these changes and gave results which agreed with those recorded above when the Wilcoxon test was used, *i.e.* a fall ($P < 0{\cdot}01$) appeared after exercise in right and left eyes, and when exercise was compared with sitting a fall was again found for right and left eyes, significantly greater for walking than sitting ($P < 0{\cdot}01$); the change which followed sitting was not significant ($P > 0{\cdot}05$).

(iii) *Effect of initial ocular tension*

Fig. 2 shows that the magnitude of the fall in ocular tension which resulted from walking was dependent on the height of the ocular tension before walking. The Spearman Rank Correlation method (Siegel, 1956) showed a significant correlation between them (right eyes $0{\cdot}01 < P < 0{\cdot}05$; left eyes $P < 0{\cdot}01$; correlation coefficients $+0{\cdot}621$ and $+0{\cdot}788$ respectively).

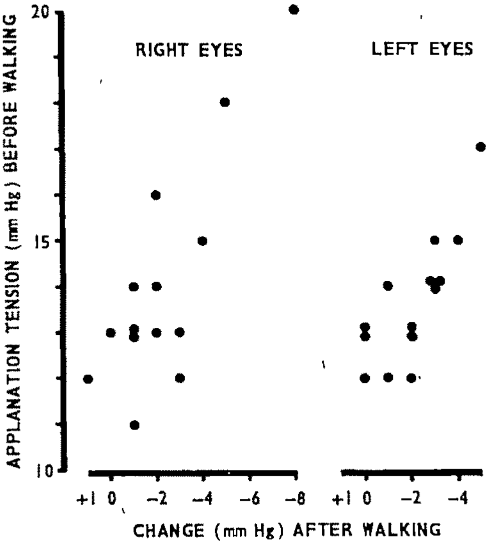

FIG. 2 *Graph of ocular tension in fourteen subjects:*

(1) *immediately before walking*

(2) *change which followed walking*

A significant correlation between 1 and 2 was present:

Right eyes $0{\cdot}01 < P < 0{\cdot}05$
Left eyes $P < 0{\cdot}01$

Correlation coefficients were $+0{\cdot}621$ and $+0{\cdot}788$ respectively

(iv) *Importance of randomization*

The effect of randomization can be seen in Fig. 3 (opposite), which shows bar charts of the mean initial (*a*) and second (*b*) applanation tensions which had been recorded on the two consecutive days, *viz.*:

I: *Not* in randomized order, *i.e.* tensions taken on Day 1 and Day 2;

II: In randomized order, *i.e.* tensions taken from seven subjects on Day 1 and from seven on Day 2.

The mean ocular tensions for Day 1 are in every case noticeably higher than those for Day 2. It is surprising that this trend is more marked in applanation readings (*b*) *i.e.* "second readings" than in the "initial readings" (*a*) (see Fig. 3). The object of the (*a*) readings was to accustom the subjects to tonometry, but as it turned out these readings would have constituted a more uniform baseline than the (*b*) readings. However, as Fig. 3 clearly shows, randomization has tended to equalize mean ocular tensions before walking and sitting, and has therefore improved the reliability of the results. Only in readings

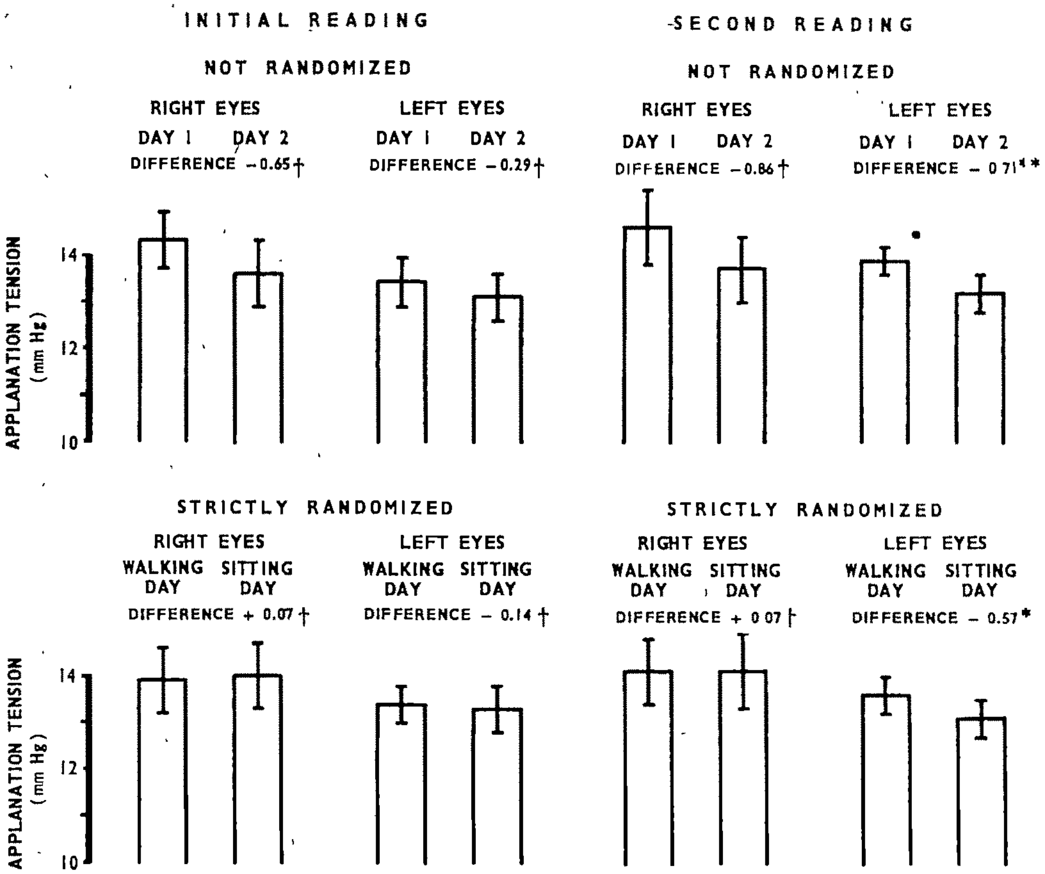

FIG. 3 *Bar charts showing effect of randomization on mean ocular tension (mm. Hg) in fourteen subjects* (i.e. *a comparison of mean initial* (a) *and second* (b) *ocular tensions*):

ABOVE *Without randomization*, i.e. *those recorded on Day* 1 *and Day* 2

BELOW *Strictly randomized*, i.e. *for the walking day and the sitting day, either of which would have been Day* 1 *for seven subjects and Day* 2 *for seven subjects*

The standard error of the mean is indicated on each bar

** difference significant at $0{\cdot}01 < P < 0{\cdot}02$ using the Wilcoxon test and Student's "t" test

* difference not significant using the Wilcoxon test ($P > 0{\cdot}05$) but significant using Student's "t" test ($0{\cdot}02 < P < 0{\cdot}05$)

† difference not significant by either test

(*b*) for left eyes was the randomization relatively ineffective in equalizing mean ocular tensions (*b*) before exercise and rest, *i.e.*

Day 1 − Day 2 : mean fall 0·71 mm.
Walking day − Sitting day: mean fall 0·57 mm.

It has already been shown (see Fig. 2) that the magnitude of the fall in ocular tension that occurred with walking was dependent on the height of the tension before walking.

If there had been a tendency for the ocular tension to fall in left eyes during sitting, this might have been masked by the relatively low ocular tension before sitting. In fact a slight rise in ocular tension was found in this case and the result was probably not seriously affected. However, if no randomization had been carried out and, say, all fourteen subjects had exercised on Day 1, then the mean pre-walking tension (*b*) on Day 1, which would be expected to be higher than the mean pre-sitting tension (*b*) on Day 2, would have biased the results in favour of a greater fall after walking than after sitting. Accordingly, without randomization, the validity of a fall in ocular tension which followed walking would have been open to some doubt. Leighton, Phillips, and Gibbs (1970), in a series of three provocative *outflow* tests on 24 subjects, showed that uniform pre-provocation values could be obtained by strict randomization in the order of performance of the tests.

Fig. 1 shows that the mean ocular tension was consistently lower in left than in right eyes. However, tension was consistently measured first in right eyes so that, in the absence of randomization, no validity can be attributed to that observation. Perkins (1959) has commented on this trend.

Mean ocular tensions (*a*) and (*b*) were consistently less for Day 2 than for Day 1, but this reached "significance" only for tension (*b*) in left eyes ($0{\cdot}01 < P < 0{\cdot}02$). Bankes, Perkins, Tsolakis, and Wright (1968) have also commented on this trend.

To sum up, it is likely that a comparison of changes in ocular tension which occurred after (*a*) walking and (*b*) sitting, carried out in randomized order at the same time of day on consecutive days, was a more reliable indication of the effect of walking on ocular tension than merely the circumstantial evidence of changes in ocular tension which occurred after walking on a particular day, *i.e.* the ocular tension might have fallen if no walking had been done. However, differences between mean tension readings (*b*) and (*c*) and between (*a*) and (*c*) on the resting day, and readings (*a*) and (*b*) on Days 1 and 2 were negligible.

No significant rise in the systolic or diastolic blood pressures after walking was found. If the change in blood pressure after sitting was taken into account, there was again no significant rise after walking.

Discussion

At first sight it might appear surprising that the ocular tension fell after exercise. The expected rise in blood pressure due to exercise might have been paralleled by an increase in ocular tension. However, such a secondary rise would probably be very transient (Duke-Elder, 1968) and the rise in blood pressure in the seven subjects in whom it was measured was slight. The systolic blood pressure was, on the average, 8·5 mm. greater after walking than after resting. The exercise was, of course, moderate in severity.

It is known that a rise in ocular tension can result from an increase in the venous pressure (Bain and Maurice, 1959; Comberg and Pilz, 1961) by constriction of the neck using an inflatable cuff. The former authors, who used a tonometer which could record the ocular tension constantly, also showed that the ocular tension could be increased by blowing against a column of mercury, coughing, and performing the Valsalva manoeuvre. They also reported a transient fall and then a rise in ocular tension on rising from a crouched (knees bend) position. They suggested that these variations in ocular tension were due to changes in venous and arterial pressure, as well as to gravity. An increase in jugular venous pressure induced in these ways could cause a rise in the episcleral venous pressure, thereby raising the intraocular pressure.

The explanation of a *reduction* in ocular tension with walking could be the opposite of this, *i.e.* a reduction in jugular venous pressure. Compensatory vascular mechanisms might be very effective and prompt, however, in reverting to a *status quo*. Measurement of the episcleral venous pressure and jugular venous pressure would be required to investigate this point.

However, we consider it quite possible that a fall in ocular tension is effected through an adrenergic or other hormonal mechanism; an effect on electrolytes or electrolyte-transport enzymes may be involved. A rise in pressure is often associated with sleep, which is presumably consistent with the fall on moderate exercise.

It cannot be assumed that, because healthy, normal subjects respond to walking by a reduction in ocular tension, adult patients with open or closed-angle glaucoma will respond similarly. If the explanation for the fall in ocular tension is a haemodynamic one, dependent on a fall in the jugular venous pressure, then the high pressure gradient between the anterior chamber and the episcleral veins in glaucoma would make a reduction in intraocular pressure less likely. On the other hand, a high *initial* intraocular pressure might be associated, as has been shown above, with a greater fall in intraocular pressure. Patients with glaucoma are to be investigated to see if they too respond to walking with a fall in ocular tension.

It would seem reasonable at present not to discourage patients who have glaucoma from walking; perhaps, on the contrary, it should be encouraged!

Summary

Fourteen adult subjects undertook walking and sitting for 50 minutes each on two consecutive mornings in randomized order. Walking and the net change produced by walking after an allowance had been made for the expected change attributable to sitting (as determined on a "control" day) both resulted in a significant fall in ocular tension. The change in ocular tension associated with sitting was, however, negligible. The higher the pressure was before walking, the greater was the fall afterwards (significant).

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Addendum Since this paper was written similar results have been reported by Stewart, Le Blanc, and Becker (1970).

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Surgery of pterygium

Modified McGavic's technique

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Pterygium must be removed if its inward growth threatens to impair vision; removal is also sometimes necessary for mechanical or cosmetic reasons. The recurrence rate may be as high as 30 to 50 per cent. (Duke-Elder, 1965) and, since such recurrences present a major surgical problem, it is important to succeed at the first attempt.

I have been using the technique of McGavic (1949) with minor modifications for the past 7 years and there have been hardly any recurrences although pterygium is so prevalent in this part of the world. McGavic originally advocated his technique for recurrent cases, but I prefer to use it at the first operation, as the method is quite safe, there is minimal postoperative discomfort, and healing is complete after only 2 weeks. In cases of recurrence the same technique may be supplemented with beta irradiation in the immediate postoperative period.

Technique

After appropriate anaesthesia, the pterygium is seized with plain forceps about 4 mm. from the limbus and horizontal incisions are made in the bulbar conjunctiva with spring scissors, cutting down to the sclera along the upper and lower borders of the pterygium away from the limbus for 12 mm. towards the canthus. Between these two incisions the pterygium is carefully dissected off the sclera with the help of blunt-pointed scissors. The apex of the pterygium is then held at its tip by toothed forceps (or by passing a stay suture through it) and is shaved completely off the cornea with a sharp cataract knife or Tooke's knife, taking care that no pterygium tissue and blood vessels are left behind. The pterygium is now held vertically taut and fine dissection is carried out to excise the whole of the subconjunctival tissue as far as the canthus. This tissue underlying the whole extent of the pterygium should come off in one triangular piece (Fig. 1). The apex of the pterygium and about 3 mm. of its body are then excised so that an area of sclera about 5 mm. wide becomes bare. The reflected conjunctiva is stroked back into position and the edges of the horizontal incisions are secured by two interrupted stitches of 000 black silk. The free edges of the conjunctival flap are then anchored firmly to the sclera with interrupted conjunctivo-scleral sutures of 000 000 black silk at intervals of 1 mm. (Fig. 2). Care is taken to include only the superficial layers of the sclera in the stitches.

Atropine and antibiotic drops are instilled and a pad and bandage are applied. Dressings are done daily. The conjunctivo-conjunctival sutures are removed on the fifth and the conjunctivo-scleral stitches on the tenth postoperative day.

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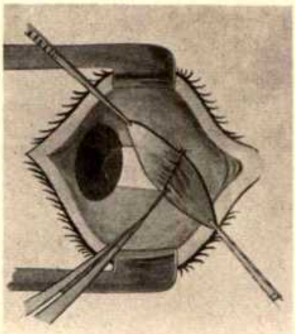
(1)



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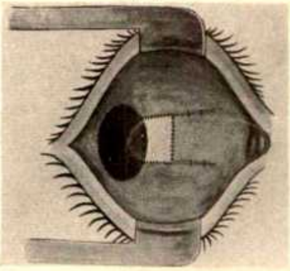

FIG. 1 *The pterygium is held vertically taut and a fine dissection is carried out to separate the underlying subconjunctival tissues which should come off in one triangular piece*

FIG. 2 *Bare area of sclera and position of conjunctivo-conjunctival and conjunctivo-scleral stitches*

Comment

At different times pterygia have been incised, removed, split, transplanted, cauterized, grafted, inverted, galvanized, heated, dissected, rotated, coagulated, repositioned, and irradiated (Trevor-Roper, 1962), but most of these methods have evoked only passing interest. The "transplantation" method is surgically not very sound. It may be hoped that after the operation, if the head continues to grow, it will merely lose itself in the oribtal tissues, but in practice the recurrence rate is about 20 to 30 per cent. (Stallard, 1958), and subsequent dissection in recurrent cases is difficult. Moreover, the procedure may at times lead to the unsightly appearance of a thick lump at the site of the transplantation. It is therefore surprising that this procedure is still being widely practised.

The recurrence rate after a simple excision is much higher, but it is often used in combination with postoperative *x* or beta irradiation (Hilgartner, Wilson, and Wilson, 1948; King, 1950; Gibson, 1951; Mead and Robertson, 1957; Lentino, Zaret, Rossignol, and Rubenfeld, 1959; Pinkerton, 1962; Cameron, 1965). This method is dangerous as even beta irradiation correctly used may damage the ciliary body and the lens. I reserve irradiation for recurrent cases and never recommend it as part of a primary procedure.

The operation described by McGavic (1949) is certainly much safer and gives very good results, but I make the horizontal incisions much longer than hitherto practised, as this greatly facilitates the subsequent dissection of the subconjunctival tissue underlying the pterygium.

As the primary focus of activity lies in the connective tissue (Kamel, 1946; D'Ombrain, 1948), total extirpation of this tissue is bound to be effective, but this step may be omitted if the pterygium is stationary and very thin and avascular, provided the paralimbal area of sclera is kept bare and the free margins of the conjunctiva are stitched to the sclera. The paralimbal scleral area is left bare to give the raw corneal surface time to heal before the conjunctiva grows up to the limbus again. If the conjunctiva is drawn right up to the limbus after any type of pterygium operation there is a danger that the free edge of the conjunctiva may adhere to the raw corneal surface with consequent early recurrence. In my experience the additional step of stitching the free margins of the bulbar conjunctiva to the superficial layers of the sclera help to prevent recurrence; these conjunctivo-scleral stitches should be placed at intervals of 1 mm. to achieve the best effect.

Summary

The extreme diversity of surgical methods for the treatment of pterygium suggests that all are to some degree unsatisfactory. McGavic's method has proved to be very effective, and the following suggestions are made:

(1) The method should be used routinely as a primary procedure;

(2) Horizontal incisions in the bulbar conjunctiva should be made much longer to facilitate dissection of the subconjunctival tissue underlying the whole extent of the pterygium.

(3) Stitches to anchor the free edges of the bulbar conjunctiva to the superficial layers of the sclera should be placed at intervals of 1 mm.

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Trachoma and increased intraocular pressure

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In trachomatous areas a large percentage of patients with glaucoma also show signs of trachoma. The WHO (1956) defined trachoma as a specific communicable keratoconjunctivitis, usually of chronic evolution, characterized by the formation of follicles, papillary hyperplasia, and pannus, and typically leading to scar formation. Contradictory reports have appeared in the literature regarding the relationship between trachoma and glaucoma. Muller (1900), DeWecker (1900), Cuénod and Nataf (1930), MacCallan (1936), Adamantiadis (1937), Sédan (1939), and Boles Carenini and Cambiaggi (1957) reported a higher frequency of glaucoma among trachomatous than among non-trachomatous subjects. On the other hand, Bailliart (1928), Terson (1928), Trantas (1937), and Pasino (1957) stated that the two conditions were independent.

This paper attempts to correlate these two diseases with reference to data extracted from a survey carried out in two villages in Northern Sudan.

Northern Sudan

The northern province of the Sudan extends between lat. 16° and 22·5° N and long. 25° and 34° E. The territory is an almost rainless desert region which suffers extremes of hot dry weather in summer and cold dry weather in winter. Sand storms prevail throughout the year but are more frequent in summer. The population, approximately one million, occupies cultivated areas separated by sparsely populated rocky and sandy areas. Atbara, the largest town in the province, is situated in lat. 17·40° N. and long. 33·59° E.

Material and methods

In 1968 the area lying between Berber town (23 miles north of Atbara) and Abuhamed town (130 miles north of Berber) became the site of a mass treatment campaign against trachoma. For assessment of the programme two villages were selected at random, Kadabas (referred to as Village A) on the western side of the river and Hafab (referred to as Village B) on the eastern side of the river. The inhabitants of both villages were examined clinically by the same ophthalmologist for signs of trachoma. All those in the age group 10 years and over were given a tonometric examination, and alternate subjects were examined by the Maklakov tonometer and the Schiotz tonometer. Only those with corneal lesions or severe inflammation and those who were very uncooperative were excluded from the tonometric examination. Cocaine 2 per cent. eye drops were used as a local anaesthetic, and patients were examined in the recumbent position. The weights used for tonometry were 10 g. in the case of the Maklakov and 7·5 g. in the case of the Schiotz tonometer. The findings were registered on special cards supplied by UNICEF. The classification recommended by WHO (1962) for trachoma diagnosis was adopted.

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In Village A 1,143 persons and in Village B 639 were examined, and there were 759 and 412 in the age group 10 years and over in Villages A and B respectively. Tonometric examination was carried out in 318 cases in Village A and in 174 cases in Village B with the Maklakov, and 341 in Village A and 211 in Village B with the Schiotz tonometer.

Results

Trachoma was significantly more prevalent in Village B than in Village A—90·8 and 68·1 per cent. (Table I). Village B maintained this higher rate in the three age groups 10–29, 30–39, and over 40 years, the rates being 87·0, 91·2, and 95·1 per cent. respectively; the corresponding rates for Village A were 64·1, 68·9, and 74·4 per cent.

Table I *Trachoma prevalence rates in Kadabas (A) and Hafab (B) villages, by age*

Age (yrs)	*Village*	*Total examined*	*Trachoma*					
			Active		*Healed*		*Total*	
			No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*
10–29	A	393	23	5·9	229	58·3	252	64·1
	B	177	16	9·0	138	78·0	154	87·0
30–39	A	132	2	1·5	89	67·4	91	68·9
	B	91	0	0·0	83	91·2	83	91·2
40 and over	A	234	1	0·4	173	73·9	174	74·4
	B	144	0	0·0	137	95·1	137	95·1
Total	A	759	26	3·4	491	64·7	517	68·1
	B	412	16	3·9	358	86·9	374	90·8

Trachoma IV cases (Table II, opposite) showed an average degree of cicatrization of 1·3 with a score of 2·1 in Village A, while Village B showed 1·5 with a score of 2·6. The percentage of cases with third degree scarring (C3) was found to be higher in Village B in all three age groups, the rate being 8·7, 15·7, and 15·3 per cent., compared with 3·5, 0·0, and 6·4 per cent. in Village A.

The mean ocular tension by age, sex, trachoma incidence, and degree of cicatrization is shown in Table III (opposite). With the Schiötz tonometer the actual reading and not the supposed equivalent in mm. Hg was recorded (Smith, 1915).

STANDARDS OF OCULAR TENSION

The generally accepted standards of ocular tension are as follows:

Maklakov	*Schiotz 7·5 weight*
18 to 21 mm. Hg within normal,	6·5 within normal,
21·1 to 24 mm. Hg suspicious,	5·5 suspicious,
24·1 mm. Hg pathological.	less than 5 pathological.

Table II *Degree of cicatrization of Trachoma IV cases in Kadabas (A) and Hafab (B) villages, by age*

Age (yrs)	*Village*	*Total examined*	*Cicatrization* C_1		C_2		C_3		*Average*	*Score*
			No.	*Per cent.*	*No.*	*Per cent.*	*No.*	*Per cent.*		
10–29	A	229	154	67·2	67	29·3	8	3·5	1·4	2·2
	B	138	94	68·1	32	23·2	12	8·7	1·4	2·4
30–39	A	89	70	78·7	19	21·3	–	–	1·2	1·6
	B	83	59	71·1	11	13·3	13	15·7	1·4	2·7
40 and over	A	173	119	68·8	43	24·9	11	6·4	1·4	2·3
	B	137	86	62·8	30	21·9	21	15·3	1·5	2·9
Total	A	491	343	69·9	129	26·3	19	3·9	1·3	2·1
	B	358	239	66·8	73	20·5	46	12·8	1·5	2·6

Note: In calculating the average degree of cicatrization C_1, C_2, and C_3 were considered to be equal to 1, 2, and 3 units respectively. The score is the deviation of the observed from the mean in terms of standard deviation.

Table III *Mean ocular tension*

Tonometer			*Malakov*				*Schiötz*			
Village			*A*		*B*		*A*		*B*	
			No. examined	*Mean tension*	*No. examined*	*Mean tension*	*No. examined*	*Mean tension*	*No. examined*	*Mean tension*
Total population			318	20·9 S.D. = 2·41	174	22·1 S.D. = 2·16	341	7·00 S.D. = 1 57	211	5·5 S.D. = 1·95
Characteristics	Sex	Male	150	20·7	74	21·4	118	7·20	85	5·90
		Female	168	21·1	100	22·9	223	6·80	126	5·30
	Age (yrs)	10–29	155	20·9	73	22·3	174	6 90	79	5·70
		30–39	64	20·6	37	21 9	59	7·00	53	5·70
		40 and over	99	21·2	64	22·0	108	6·90	79	5·20
	Trachoma	O	98	20·8	22	22·4	109	7 00	16	5 50
		IV	220	21·0	152	22·2	232	6·90	195	5·50
	Degree of cicatrization in Tr IV cases	C_1	158	20·8	102	21·9	159	6·9	132	5 6
		C_2	55	21 3	36	23·2	53	7·1	33	5·8
		C_3	7	23·3*	14	22·6	20	6·8	30	5 0

*One patient aged 75 years gave ocular tensions 31 and 35 for the right and left eyes; excluding this case the mean tension would have been 20·9

In the Sudan the mean ocular tension has not been studied before. It was found in this survey that the mean tension with the Maklakov tonometer was 20·9 mm. Hg (standard deviation ± 2·41) in Village A and 22·1 mm. Hg (S.D. ± 2·16) in Village B. The difference is significant, being 5·7 times the standard error (S.E. ± 0·21).

Using the Schiötz tonometer, Village A had a mean reading of 7·00, equivalent to 20·2 mg. Hg (standard deviation ± 1·57). Village B had a mean reading of 5·5, equivalent to 25·3 mm. Hg (standard deviation ± 1·95). Again the difference is significant, being 9·5 times the standard error (S.E. ± 0·16).

Taking each village separately, the mean tension did not vary with age or trachoma incidence.

The females in the two villages showed a slightly higher tension than the males; this tendency was more marked in Village B: 21·4 mm. Hg for males and 22·9 mm. Hg for females, the corresponding Schiötz readings being 5·9 (=24·5 mm. Hg) and 5·3 (=27 mm. Hg).

The females in the two villages also showed a higher prevalence of trachoma, again more marked in Village B. The rates were 57·8 per cent. in Village A and 60·6 per cent. in Village B for females, and 42·2 and 39·4 per cent. respectively for males.

The mean ocular tension was studied in relation to the degree of cicatrization in TR IV cases, and it was found that cases with third degree cicatrization (C_3) exhibited a higher mean than those with first degree (C_1); this too was more apparent in Village B (Table III).

In this survey all our measurements are on the high side, which is probably due to the fact that we used cocaine drops as a local anaesthetic and measured the tension while the patient was in the recumbent position. Cases with an increased tension in both villages were tabulated according to the generally accepted standards of ocular tension: over 24 mm. Hg with the Maklakov tonometer and less than 5 with the Schiötz tonometer (Table IV, cols 4 and 5), and also those with a pathologically high tension: over 28 mm. Hg and less than 3 (Table IV, cols 6 and 7). The findings all follow the same pattern. The percentage of cases with a pathologically high tension was 1·1 per cent. in trachoma-free cases and 4·1 per cent. in persons with trachoma, while a moderately high tension was observed in 7·1 and 18·5 per cent. respectively. The incidence of high tension increased with age, the increase being statistically more significant in persons with trachoma.

Table IV *Incidence of high and pathologically high ocular tension in persons examined in both villages*

Trachoma stage	*Age (yrs)*	*Total examined*	*Persons with high tension*			
			Over 24 mm. Hg or less than 5		*Over 28 mm. Hg or less than 3*	
			No.	*Per cent.*	*No.*	*Per cent.*
O	10–29	164	9	5·5	1	0·6
	30–39	49	5	10·2	0	0·0
	40+	67	6	9·0	2	3·0
	Total	280	20	7·1	3	1·1
IV	10–29	367	51	13·9	5	1·3
	30–39	172	32	18·6	10	5·8
	40+	310	74	23·9	20	6·5
	Total	849	157	18·5	35	4·1

These observations may be summarized as follows:

(1) Trachoma was more prevalent in Village B.

(2) The mean tension was higher in Village B.

(3) Females showed a higher trachoma rate and a higher mean tension than males.

(4) The degree of cicatrization was greater in Village B.

(5) The mean tension was higher in those with third degree than in those with first degree cicatrization.

(6) Pathologically high tension was mainly associated with the presence of trachoma.

Discussion

The villages in the Northern Sudan and their inhabitants all look very much alike in almost every respect. One village may differ from another only in its proximity to the river and hence in the ease of obtaining water. This will naturally have an effect on the incidence and severity of trachoma. In this survey both trachoma and the mean ocular tension was significantly more prevalent in Village B.

Cuénod and Nataf (1928) found that at least 75 per cent. of glaucomatous patients in Tunisia exhibited signs of trachoma. Nema, Saiduzzafar, Nath, and Shukla (1964) found a significantly higher mean ocular tension in trachomatous than in non-trachomatous subjects. The higher mean ocular tension found in Village B in all age groups and in both sexes as compared to Village A is very striking, especially as Village B also has the higher trachoma index. Cuénod and Nataf (1930) found that the frequency of glaucoma was 3 per cent. among trachomatous cases and only 1 per cent. among non-trachomatous cases. Boles Carenini and Cambiaggi (1957) found that the incidence of glaucoma was nearly 10 per cent. among trachoma-free patients. Sie Boen Lian (1956) found 17 per cent. with pathologically raised tension. In this survey the incidence of glaucoma was 4·1 per cent. among trachomatous cases and 1·1 per cent. among non-trachomatous cases.

The trachoma index, taking both villages together, was 76·1 per cent., but among glaucoma cases it was 92·1 per cent. Casanovas and Mawas (1961) believed that, where many cases of glaucoma show signs of trachoma, the latter can be considered as one of causative factors.

Not a single case of acute glaucoma was observed in this series. In South Tunisia, an area with a high trachoma index, Kolin (1965) remarked upon the predominance of open-angle glaucoma over closed-angle glaucoma (5·5 and 1·0 per cent. respectively). It is generally accepted that the trachoma agent as such does not cause a rise in ocular tension, and therefore if glaucoma occurs it would be the result of cicatrization. Ashton (1960) observed that structural changes in the trabecular meshwork were of possible importance in the pathogenesis of primary glaucoma. Blatt (1961) found glaucoma in subjects in the later stages of trachoma.

It was not possible under field conditions for us to study the aqueous veins, but Boles Carenini and Cambiaggi (1957) saw fewer aqueous veins in eyes affected by trachomatous pannus and concluded that this was an indication of obliteration of the limbal and prelimbal vessels. Luntz and Smith (1960) found fibrosis of the episcleral tissue around the limbus leading to obliteration of the episcleral veins in four Negroes.

It seems that trachoma causes a rise in ocular tension only in special cases in which there is obliteration of the prelimbal and scleral outlets (Sie Boen Lian, 1965). Re-infection with trachoma is common and with each attack further cicatrization may be expected. This explains the higher incidence of glaucoma among trachomatous cases with advancing age; 1·3, 5·8, and 6·5 per cent. in the age groups 10–29, 30–39, and over 40 years respectively. Kamel (1963) incriminated repeated re-infections as an aetiological factor in the causation of primary glaucoma, and suggested that once cicatrization of the lid was complete re-infection tended to involve the bulbar conjunctiva.

It is true, of course, that primary glaucoma is a disease of the older age groups. According to Luntz, Sevel, and Lloyd (1965), high intraocular pressures are not often found below the age of 50 years. Kamel (1963) observed the comparatively very early age at which glaucoma occurs in the United Arab Republic where the trachoma index is high. We have found pathologically high intraocular pressures in the age group 30–39 years and even at 10 to 29 years in trachoma patients, whereas the non-trachomatous glaucoma cases all occurred in the age group 40 years and over (except one case in Village B recorded in a youth aged 19 years).

Summary

A survey of glaucoma and trachoma in the Northern Sudan suggests that trachoma may cause the intraocular pressure to rise as a result of cicatrization.

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Systemic absorption of Soframycin after subconjunctival injection

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Soframycin* is a member of the neomycin group of aminoglycoside antibiotics. Neomycin as used clinically is a mixture of neomycins B and C, whereas Soframycin is thought to be neomycin B itself (Garrod and O'Grady, 1968). It has been established experimentally that both neomycin (Sorsby and Ungar, 1960) and Soframycin (Ainslie and Henderson, 1958) penetrate well into the aqueous humour after subconjunctival injection, and both drugs are used clinically by this route to combat severe ocular infection by a wide range of organisms (Ainslie and Cairns, 1960).

The chemical relationship between neomycin and Soframycin is such that neither drug should be administered systemically except to save life. The possibility that neomycin given subconjunctivally might cause systemic toxicity has been considered, (Sorsby and Ungar, 1960), but no data exist for the systemic absorption of this drug or of Soframycin after subconjunctival injection in man. This paper reports the levels of Soframycin reached in the blood after subconjunctival injection, and the significance of these findings is discussed in relation to available information on systemic toxicity.

The literature on neomycin toxicity is extensive. Systemic neomycin is ototoxic, nephrotoxic, and occasionally vestibulotoxic. In the presence of renal disease excessively high serum levels of the drug may follow systemic administration, so that the risk of ototoxicity is increased.

Deafness may follow a wide range of doses, the old and the young being equally vulnerable, and individual susceptibility plays an important part. A striking feature of the ototoxicity is the interval between the start of therapy and the onset of hearing loss.

The lag is such that deafness may be complained of as long as 1 to 4 weeks after stopping the drug (Halpern and Heller, 1961; King, 1962; Leach, 1962). Leach has suggested that there is a gradual build-up of the drug in the endolymph when administration is prolonged for more than a few days. It is relevant that significant levels are found in the cerebrospinal fluid after systemic therapy. Waisbren and Spink (1950) found a level of 1·26 μg./ml. in one patient receiving 1 g. neomycin daily by intramuscular injection.

Once hearing loss has begun there may be a down-hill progression over a period of 1 to 3 months (Waisbren and Spink, 1950; Halpern and Heller, 1962) and possibly longer (Leach, 1962). This deterioration continues despite stopping the drug. Deafness may be total and is clinically irreversible, although reversible lesions in the organ of Corti have been noted in the guinea-pig (Friedman, Dadswell, and Bird, 1966).

Hawkins and Lurie (1953) demonstrated in the cat that mild ototoxicity is associated with degeneration of the external hair cells of the organ of Corti followed later by degenera-

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*Soframycin is the proprietary name for framycetin sulphate, manufactured by Roussel Laboratories.

tion of the internal hair cells. The earliest changes occur in the basal turn of the cochlea and this correlates with the clinical manifestation of a high-tone perceptive deafness.

The studies of Massénat-Déroche (1954) showed that Soframycin was similarly able to produce auditory damage after parenteral use.

Material and methods

The subjects in this study were patients undergoing routine intraocular surgery (mainly cataract extraction) who received a prophylactic injection of 250 mg. Soframycin in 0·5 ml. sterile water at the end of the operation; 33 patients, nineteen men and fourteen women, were studied. The mean age was 61 years (range of 13 to 81). The subconjunctival injection was delivered into the lower fornix. One patient underwent surgery under local anaesthesia, which included a retrobulbar injection of lignocaine and adrenaline and topical cocaine to reinforce surface analgesia. The remaining patients underwent general anaesthesia.

Blood was taken from patients just before subconjunctival injection and again at approximately 1, 3, and 6 hrs afterwards. In seventeen of the patients, later blood samples were obtained. Blood was collected in screw-cap bottles, allowed to clot at room temperature, and centrifuged, and the serum was pipetted into bijou bottles for storage at −40°C.

In twelve of the patients, a preoperative urine sample was collected, and a further postoperative 24-hr urine sample was obtained and the volume measured. An aliquot of each specimen was stored at −40°C.

Serum and urine specimens were sent in batches for bioassay to Roussel laboratories, where assays were carried out under the direction of Mr. R. C. Strange.

BIOASSAY

Assay of Soframycin in serum and urine samples was carried out by a standard cup diffusion method, using *Bacillus subtilis* as test organism. Standard solutions and test dilutions were made with 0·1M (pH 7·9) phosphate buffer solution. Standards were made up to contain 10; 5; 2·5; 1·25, and 0·625 µg./ml. In the system used it has not been found necessary to make a correction for plasma-binding. Pre-treatment serum or urine specimens were assayed undiluted and as 1 : 1 and 1 : 4 dilutions. After treatment samples were assayed undiluted and as 1 : 4, 1 : 9, and 1 : 19 dilutions.

The diffusion plates were prepared as a base layer of agar containing a suspension of *B. subtilis* spores. A series of 64 7-mm. diameter cups was punched out from each plate to form a latin square, 8 × 8. Dilutions of test and standard were pipetted into the cups within the diffusion plate and inhibition zones were read after 18 hrs' incubation at 30°C. Quadruple samples of each dilution of test and standard were included in each plate, to exclude errors in assay due to uneven preparation of the plate. Zone diameters within a group were accepted only if they agreed to within 0·2 mm. of their mean. Standard curves were prepared for each plate by plotting zone diameters of standards against $\log_{10}$ antibiotic concentration and the antibiotic concentration of test solutions were read off the curves and corrected for dilution. The assay is accurate to within ±5 per cent.

Results

A total of 33 patients received 250 mg. Soframycin subconjunctivally. In three there were errors in blood sampling and the results were discarded. In 22 of the remaining thirty patients, serum Soframycin levels were available for the 1 to 1½ hr periods and these were grouped together as the "peak" serum levels. In three of these subjects no activity was recorded in the serum at any time and therefore these results were not included in deriving the mean. The mean peak serum level was 5·07 µg./ml. (with a standard deviation of 2·02 µg./ml.) The serum levels of Soframycin after injection are plotted in the Figure. Values obtained beyond 9 hours after injection are not plotted. The maximum peak

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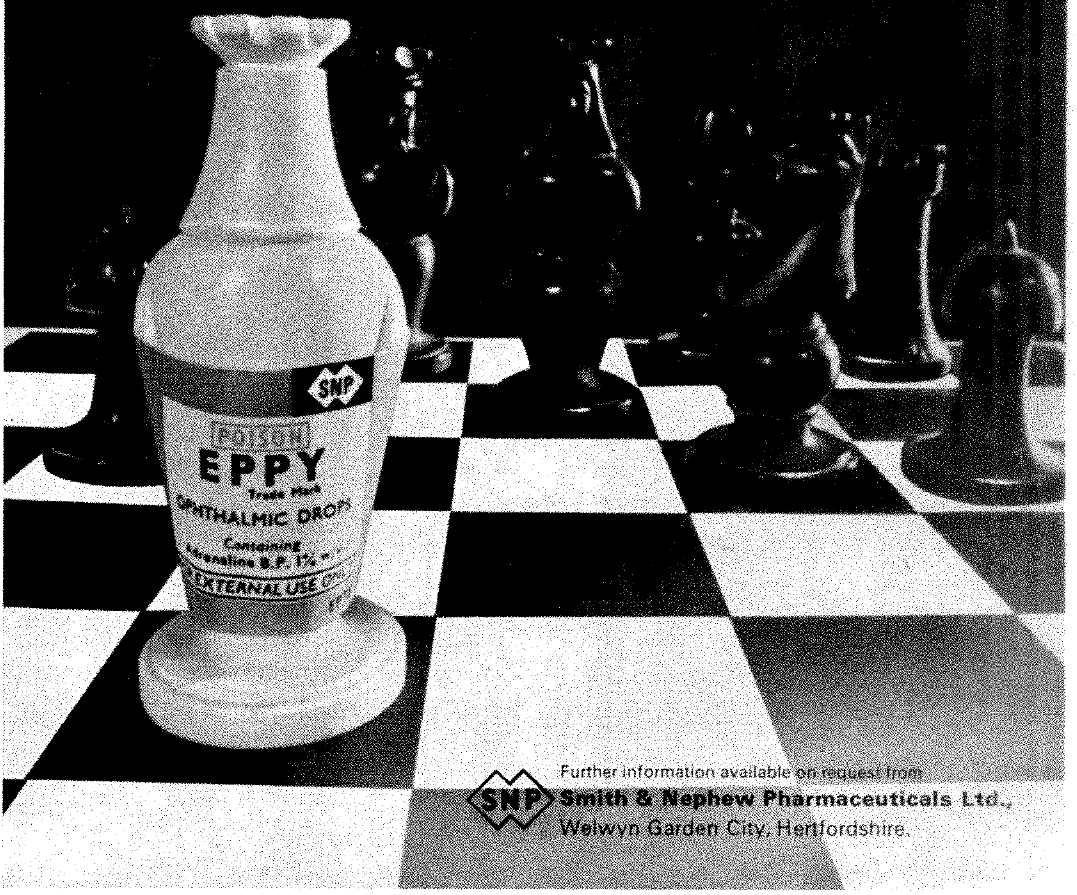

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References

1. *Brit. J. Ophthal.* (1955), **39,** 557
2. *Brit. J. Ophthal.* (1956), **40,** 159
3. *Brit. J. Ophthal.* (1965), **49,** 98

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serum level recorded was 9·6 µg./ml. and the minimum detectable peak level was 0·6 µg./ml. In three patients no antibiotic activity was detected at any time within the first 6 hrs. In no subject was antibiotic activity detected in the preinjection serum sample.

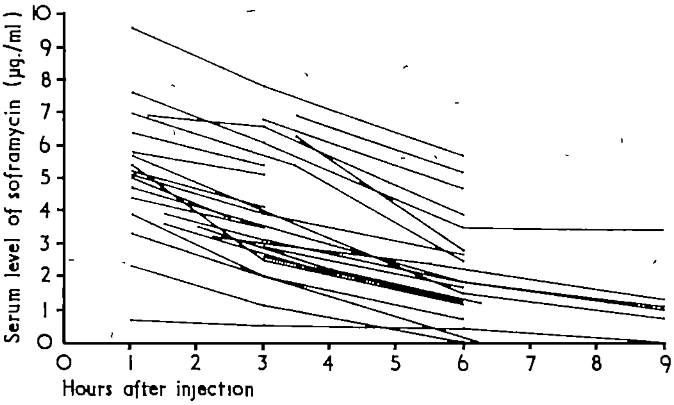

FIGURE *Serum levels of Soframycin (µg./ml.) after subconjunctival injection in 22 cases*

In the seventeen patients, from whom blood was taken later than 6 hrs after injection, the data are patchy but some useful information is available. In five patients, detectable levels of Soframycin were present at 9 hrs. In three of these, levels of 0·53, 0·57, and 1·1 µg./ml. respectively were present as late as 12 hrs after injection. In one subject, Soframycin was detected at a concentration of 1·2 µg./ml. at 25 hrs. In the remainder there was no detectable level from 20 to 29 hrs after injection.

A plot of body weight against peak serum levels suggested that a negative correlation might exist between these parameters. However, the correlation coefficient was not found to be statistically significant ($r = -0{\cdot}383$; $P > 0{\cdot}05$:). The urinary excretion of Soframycin was measured in twelve subjects. The Table shows the excretion of Soframycin expressed as a percentage of the dose injected subconjunctivally. The maximum recorded percentage was 33·8 and the minimum 0·9. In this last subject, and in another in whom only 2 per cent. of the injected dose was excreted, no serum levels of antibiotic were detected.

Table *Percentage of subconjunctivally-injected Soframycin excreted in the urine in 24 hours*

Urine volume (ml.)	*Soframycin concentration (µg./ml.)*	*Amount excreted (mg.)*	*Percentage excreted*
850	24·6	21·8	12
600	2·6	1·6	1
700	33·5	23·3	13
450	94·0	42·3	24
880	4·1	3·6	2
400	82·8	33·0	19
250	36·6	9·1	5
700	78·5	54·6	30
410	146·1	60·0	34
230	113·2	27·0	15
250	129·6	32·4	18
450	72·4	32·2	18

Urinary Soframycin concentrations are expressed as base. Percentage excretion is calculated assuming that 1,000 mg. framycetin sulphate is equivalent to 710 mg. of base.

Discussion

These results demonstrate that there is a substantial absorption of subconjunctivally-injected Soframycin into the bloodstream. The high serum levels recorded were of a similar order to those reported by Massénat-Déroche (1954) after the intramuscular injection of 250 mg. framycetin sulphate in adult subjects. In his study, peak levels were reached in 1 hr and the mean peak value in six subjects was 6·5 μg./ml.

In the present study Soframycin was undetectable in the bloodstream of the majority of patients 24 hrs after injection; in a few, it was undetectable after only 6 hrs. Though the variation is great, it can be stated that the persistence of the antibiotic in the bloodstream is of a similar order after subconjunctival injection to that found after intramuscular injection.

It may be noted that the highest serum level reported by Massénat-Déroche was 20 μg./ml., over twice the maximum level found in the present study. When it is recollected that most of the patients in this study underwent cataract extraction and that this involved opening the conjunctiva, it is clear that the opportunity would exist for loss of a proportion of the injected antibiotic into the conjunctival sac, and a reason for the lower levels found here is provided. Some support for this suggestion is given by the urinary excretion values, which were also on the low side. The maximum 24-hr percentage excretion was 33·8 per cent. Leach (1962) stated that, in patients with normal renal function, a single intramuscular dose of neomycin is rapidly excreted in the urine in 6 to 8 hrs and is completely cleared from the body in 24 hrs. It is not possible to say what is the effect of general anaesthesia on the renal handling of the injected Soframycin, but this may also have been a factor modifying serum levels.

It is likely that in the therapeutic situation, with the conjunctiva intact, higher serum levels of antibiotic might be expected which would approximate to those seen after intramuscular injection. Though the aim of subconjunctival injection is to achieve a high local concentration of the antibiotic in the eye, the degree of systemic absorption is sufficient to regard it as simply another form of parenteral injection with the same implications of systemic toxicity.

Although the bulk of cases of neomycin toxicity followed its early use as an intramuscular injection, there is evidence of significant systemic absorption and of toxicity after the administration of the drug by a number of other routes. Poth, Fromm, Wise, and Hsiang (1950) recorded a patient with ulcerative colitis who was given neomycin by mouth in a dose of 0·1 g./kg. daily, in whom serum levels up to 3 μg./ml. were achieved. In this subject, 3 per cent. of the total oral dose was excreted in the urine. Halpern and Heller (1961) reported an adult who developed bilateral auditory impairment after 585 g. neomycin given orally to produce intestinal sterilization in hepatic coma. Last and Sherlock (1960) reported deafness in a similar patient receiving 560 g. neomycin daily for hepatic failure. The serum neomycin on the day on which deafness developed was 0·4 μg./ml., but in view of the lag between dosage and the first clinical manifestations of the toxic effects, it would be unwise to give special significance to this figure. Fuller (1960) reported deafness in two children using neomycin aerosol for staphylococcal pulmonary infection. The period of medication exceeded 2 years in each case though extending over a greater length of time. Campanelli, Grimes, and West (1966) reported hearing loss in a 5-year-old child who received irrigation of an infected knee sinus with a solution of 10 per cent. neomycin over a period of 9 days (approximately 240 g. neomycin being delivered to the joint).

Deafness after the irrigation of empyema cavities has been reported by a number of workers, and of particular interest is the report of Helm (1960) of deafness in an adult after four weekly intrapleural injections of 1 g. neomycin, only 4 g. neomycin in all.

It is not possible to find in the literature the levels of neomycin in the bloodstream which may be regarded as toxic. It does not appear to be known for how long a minimum serum level must act to produce toxic effects in man and the absolute toxic level is also not known. For this reason, it is difficult to define a safe subconjunctival injection regime for Soframycin or indeed for any drug which is potentially systemically toxic. On the other hand, Soframycin is of proven therapeutic value in the treatment of ocular infection and after over 10 years of clinical use no report of systemic toxic effects has been made. It would be rash to modify clinical use without such evidence, and obviously similar considerations would apply to other ototoxic drugs, such as streptomycin, kanamycin, vancomycin, and gentamycin; particularly when, like kanamycin and vancomycin, they are also nephrotoxic.

Sorsby and Ungar (1960) have cautioned against the use of more than four consecutive daily doses of 500 mg. each of neomycin subconjunctivally because of the toxic potential of the drug. In the absence of any information to the contrary it would appear safe to employ a similar regime for the adult patient using Soframycin. On the other hand, in those circumstances where it might be expected that such a regime would produce unduly high serum levels, dosage should be modified. This is the case in patients with renal disease, and in infants and children.

In the presence of renal failure, systemically absorbed neomycin shows a cumulative rise with repeated dosage (Last and Sherlock, 1960). It would be simple to measure blood urea in patients about to receive multiple subconjunctival injections of Soframycin and, in the presence of renal failure, to monitor serum levels of the antibiotic and adjust subsequent dosage accordingly.

Similar arguments would suggest modification of the dose of subconjunctival Soframycin in children, where the full adult subconjunctival dose would represent a proportionately larger body weight dose. A higher and more sustained level of the antibiotic in the bloodstream would be anticipated than in the adult. It is salutary to recall that ototoxicity has been recorded with an oral dose of as little as 2 g. neomycin given to an infant treated for viral enteritis (King, 1962). This dose is equivalent to four 500-mg. subconjunctival injections, and one may assume that absorption from the subconjunctival space is greater than from the gastrointestinal tract.

In further studies it is intended to measure serum levels after the injection of 500 mg. doses subconjunctivally. The effect of combining adrenaline with the injection will also be examined. It is common to include adrenaline in the solution for injection to increase local absorption and prolong the persistence of the antibiotic in the eye (Sorsby and Ungar, 1960). Experimentally it can be shown that adrenaline also results in lower antibiotic levels in the bloodstream after subconjunctival injection (Sorsby and Ungar, 1947). In clinical use such an effect would be of value in reducing systemic toxicity. It is also intended to carry out a prospective study of audiometric performance in patients receiving subconjunctival Soframycin in order to detect subclinical ototoxicity.

Summary

(1) The systemic absorption of Soframycin after the subconjunctival injection of 250 mg. has been studied in patients after routine intraocular surgery.

(2) The levels reached in the bloodstream are of a similar order to those seen after intramuscular injection. The mean peak serum level was 5·07 µg./ml. and the maximum recorded was 9·6 µg./ml. In the majority of patients the antibiotic was undetectable in the serum 24 hrs after injection.

(3) In view of these findings and since Soframycin is potentially an ototoxic, nephrotoxic, and vestibulotoxic drug, it is suggested that ophthalmologists should use a lower dose regime for infants and children and that extra caution should be exercised in the treatment of patients with impaired renal function.

(4) There appears to be no need to alter the recommended dose regime in adults in the absence from the literature of definite reports of systemic toxicity.

It is a pleasure to record our thanks to Dr. A. Atkinson and Mr. R. C. Strange of Roussel Laboratories for their collaboration in the study, as well as to Mr J. R. Sendak who performed the statistical analysis. Our thanks are also due to Prof. B. R. Jones for discussion and criticism of work in preparation.

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Brit. J. Ophthal. (1970) 54, 621

Anterior lenticonus and the Waardenburg syndrome

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Blackburn, Lancs.

Anterior lenticonus is a rare condition in which there is a conical forward protrusion of the axial portion of the anterior capsule of the lens and anterior cortex which usually remains clear. The nucleus is not involved, indicating that the anomaly develops relatively late. Males are more commonly affected than females and in most cases both eyes are involved. Some of the cases reported in the literature are associated with Alport's syndrome, which comprises hereditary chronic progressive nephritis and perceptive deafness and is usually transmitted as an autosomal dominant trait (Arnott, Crawfurd, and Toghill, 1966).

In the patient reported below bilateral anterior lenticonus is associated with the Waardenburg syndrome, a feature of which is hereditary perceptive deafness, and which also has an autosomal dominant mode of inheritance. According to Duke-Elder (1964) some cases may occur sporadically.

Case report

A man born in 1946 first attended the out-patients department in February, 1967, complaining of progressive deterioration of the visual acuity in each eye and increasing deafness for several months. There was no past or recent history of head or ocular injury, or of ocular or otological disease. He had had uncomplicated mumps at the age of 15 years but there was no other significant medical history. No members of his family were known to suffer from deafness. His paternal grandmother had senile cataracts.

Examination

He had a well-marked white forelock. The fronto-nasal angle was absent, the root of the nose was broad and prominent, and the eyebrows were confluent across the prominence (synophrys). Although the root of the nose was broad the internal canthi were not displaced laterally and the lower lacrimal puncta were in normal apposition to the eyeballs. His hearing was impaired and he appeared to lip-read with difficulty.

Biomicroscopy of the right eye showed a small vesicle beneath the axial portion of the anterior capsule which was pushed forward as a conical projection into the anterior chamber. Behind the vesicle was a localized anterior polar cataract. The lens nucleus was not involved and was clear. The visual acuity was 6/60.

The left eye showed a small rupture in the anterior capsule, in the lower outer quadrant of the lens approximately 3 mm. away from the optic axis, through which opaque lens cortex was extruded into the anterior chamber. The visual acuity was reduced to hand movements at one metre.

Each cornea showed a well-defined arcus juvenilis. There was no evidence of uveitis in either eye. Apart from a small benign melanoma of the iris of the right eye there was no disturbance of iris pigmentation nor any evidence of hypoplasia of the iris stroma.

The Wassermann reaction, gonococcal complement-fixation test, and Price's precipitation reaction were negative.

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Investigations

Pure-tone audiography confirmed a severe bilateral perceptive deafness (Figure).

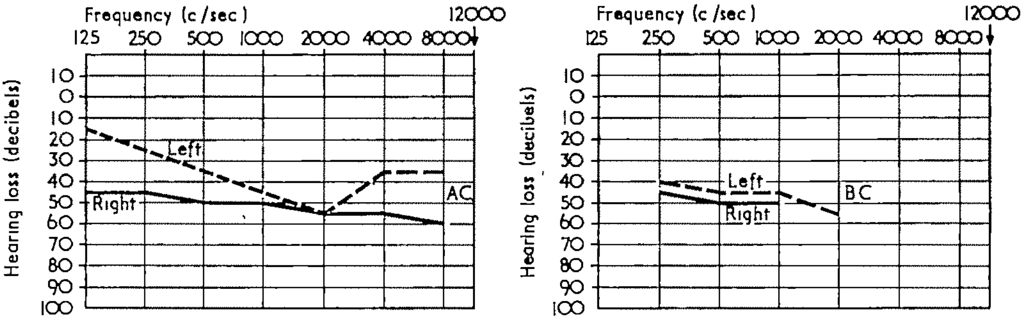

FIGURE *Audiogram* 22.2.67, *showing bilateral severe perceptive deafness. There was no bone conduction after* 2,000 *c/sec.*

Haemoglobin 118 per cent. Erythrocyte sedimentation rate 3 mm./1st hr (Westergren). Serum proteins 6·9 per cent.; albumin 3·5 per cent.; globulin 3·4 per cent.; A/G ratio 1·03 : 1. Serum cholesterol 198 mg./100 ml. Toxoplasma dye test positive at a dilution of 1 : 8.

X rays of the chest and paranasal sinuses normal. Urine analysis normal.

Progress

The patient was admitted to hospital for observation and treatment. One week after admission the anterior lenticonus of the right lens ruptured spontaneously and the anterior polar cataract was immediately extruded into the anterior chamber. Thereafter the lens of each eye developed total cataract which absorbed slowly over a period of 5 months.

Treatment

He was re-admitted to hospital in July, 1967, and a discission of the posterior capsule of the right eye was performed. The visual acuity of this eye improved to 6/9, with +12 D sph., +0·5 D cyl., axis 90°. Discission of the posterior capsule of the left eye followed and the visual acuity of this eye also improved to 6/9 with a spectacle lens of the same power. The gap obtained in the posterior capsule of the left eye was small and some proliferation of the capsular epithelium necessitated a second discission. This was carried out during January, 1970, and was followed by restoration of 6/9 vision.

Discussion

Arnott and others (1966) reviewed 42 cases of anterior lenticonus reported in the literature and added a new case of their own. Twelve of the reported cases (28 per cent.) were associated with Alport's syndrome. Anterior lenticonus, or indeed any other form of lens anomaly, has not been hitherto described in association with the Waardenburg syndrome which, when fully expressed, comprises the following features, listed in order of the degree of penetrance from high to low (Waardenburg, 1951):

(*a*) Lateral displacement of the inner canthi,
(*b*) Broadness and prominence of the root of the nose,
(*c*) Confluence of the eyebrows,
(*d*) Heterochromia iridum,
(*e*) Congenital perceptive deafness, and
(*f*) White forelock.

The feature common to the two syndromes is perceptive deafness. Ocular defects are not uncommonly found in association with syndromes of deafness of either genetic or congenital origin. In the syndromes under discussion, disturbances of the ocular neuroectoderm, hypoplasia of the iris stroma, and hypopigmentation of the fundus (Hass and Tan, 1966) are linked with perceptive deafness in the Waardenburg syndrome, and anomalies of the lens, anterior and posterior lenticonus, lentiglobus, and spherophakia are linked with Alport's syndrome. The case described differs from the usual pattern—a lens anomaly is involved in the Waardenburg syndrome in which the expected ocular defect is an abnormality of uveal pigmentation—and this is probably a chance occurrence. In this case there was no hereditary element and the syndrome was incompletely expressed, in that dystopia of the inner canthi and heterchromia iridum were not present. The other features of the syndrome were definite and the perceptive deafness was severe.

Probably the most interesting feature of this case is the spontaneous rupture of the lens capsule, a rare event which has so far been described in detail in only two patients with anterior lenticonus (Ehrlich, 1946; Gregg and Backer, 1963). The lens capsule in cases of anterior lenticonus has been found to be thinned and stretched, the number of epithelial cells being less than normal (Duke-Elder, 1964), and this accounts for the ease with which spontaneous rupture occurs. The cause of the defect is still a matter for conjecture.

Comparing his case with those described by Jaworski (1910), Tsukahara (1930), and Feigenbaum (1932), in which anterior polar cataracts developed, Ehrlich (1946) suggested that a self-healing spontaneous rupture of the lenticonus probably accounted for the change from anterior lenticonus to anterior polar cataract. However, the present case and that described by Gregg and Becker (1963) demonstrate that an anterior polar cataract can antedate the rupture of the lenticonus.

The remaining feature of interest is the arcus juvenilis, the significance of which is not clear. There was no evidence of degenerative corneal disease or hypercholesterolaemia. The case of anterior lenticonus and Alport's syndrome described by Arnott and others (1966) also had this feature and they observed that it was also present in a similar case described by Tsukahara (1930).

Summary

A case of bilateral anterior lenticonus with spontaneous rupture of the anterior lens capsule is described and compared with two other reported cases of this rare anomaly. The lens defects were associated with the Waardenburg syndrome.

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Removal of a foreign body from the back of the orbit

F. J. CURTIS AND D. H. PROVAN

East Surrey Hospital, Redhill

The removal of deeply-embedded foreign bodies always presents a problem. The following case is reported to illustrate a technique used in a small provincial hospital without the aid of elaborate equipment. The standard *x*-ray screen was used, and the procedure would undoubtedly have been easier if an image intensifier had also been available.

Case report

A boy aged 13 was brought to the casualty department on May 15, 1969. He had been shooting at a tin with an air-gun and had received a severe blow over the left eye. He was found to have a small round puncture wound immediately below the inner end of the left eyebrow in the trochlear region, with slight swelling of the upper lid and the left bulbar conjunctiva. He was complaining of diplopia and there was limitation of movement of the eye in all directions.

Examination

Radiography revealed a lead air-gun pellet in the back of the orbit (Fig. 1*a*, *b*).

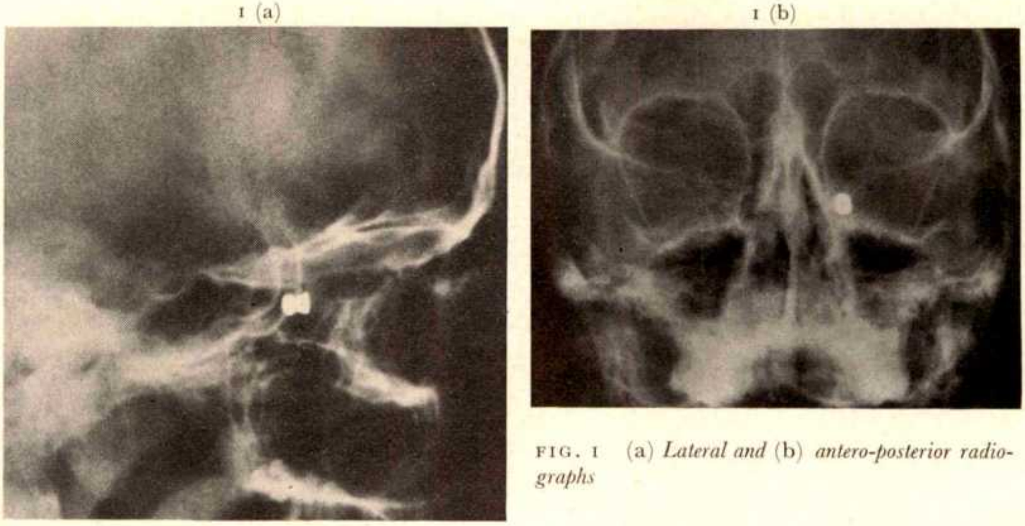

FIG. 1 (a) *Lateral and* (b) *antero-posterior radiographs*

He was admitted to the Eye Unit where the puncture wound was confirmed. By this time there was more marked chemosis and limitation of all movements, with horizontal diplopia. Further localizing *x* rays revealed that the pellet was lying just nasal to the optic foramen, approximately 5 cm. from the orbital margin (Fig. 2, opposite).

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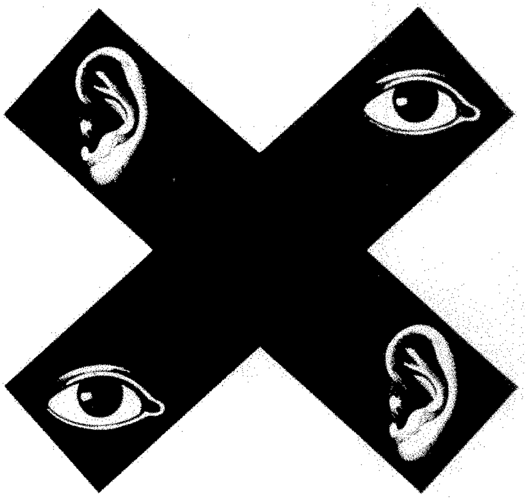

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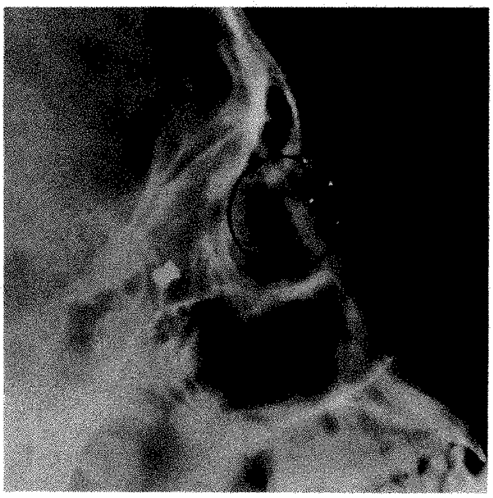

FIG. 2 *Localizing radiograph with contact lens* in situ. *Circle represents size and position of eyeball*

Operation

Under general anaesthesia on the x-ray table, using a standard screen, a probe was found to pass easily through the puncture wound and along the track under radiographic guidance until the pellet could be felt. Measurements of depth and direction were confirmed and the probe was replaced by a Hartman's aural crocodile forceps. With similar radiographic guidance the forceps was passed up the track and after very careful feeling it was possible to grip the skirt of the pellet and gradually to withdraw it. It was necessary to enlarge the skin wound slightly in order to extract forceps and pellet together. 2 ml. penicillin were then injected along the track and the patient returned to bed.

Postoperatively there was remarkably little reaction, but when the dressing was removed there was found to be total diplopia and complete absence of any adduction of the left eye. Treatment was given with local short-wave therapy.

A Hess screen test (Fig. 3) 4 days later showed complete paralysis of the left medial rectus and secondary overaction of the right lateral rectus. Active duction exercises were given.

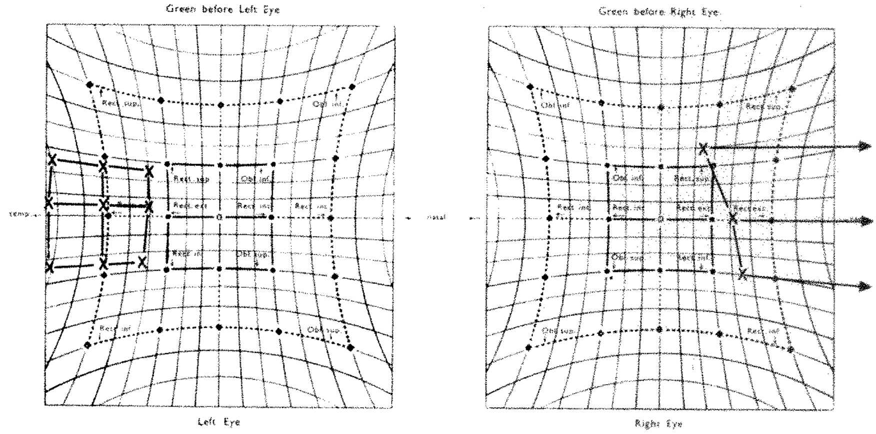

FIG. 3 *Hess charts 4 days after removal of foreign body from left orbit*

Progress

On the eighth day he was sent home with a patch for covering each eye alternately. On June 5, 1969 the visual acuity in the right eye was 6/5, and in the left 6/9; there was a variable left divergent squint of 20° to 50° with no left adduction. He was instructed to persist with duction exercises for 2 minutes every half hour, and was allowed to return to school on the understanding that he was to be given rest periods mid-morning and mid-afternoon.

By June 26 he had regained binocular single vision to the left and almost to the straight ahead position, and was managing to carry on all day at school. The visual acuity had improved to right and left 6/4 and he could move his eye fully in all directions, but it required an effort to maintain binocular single vision to the right. The Hess screen test (Fig. 4) showed this great improvement.

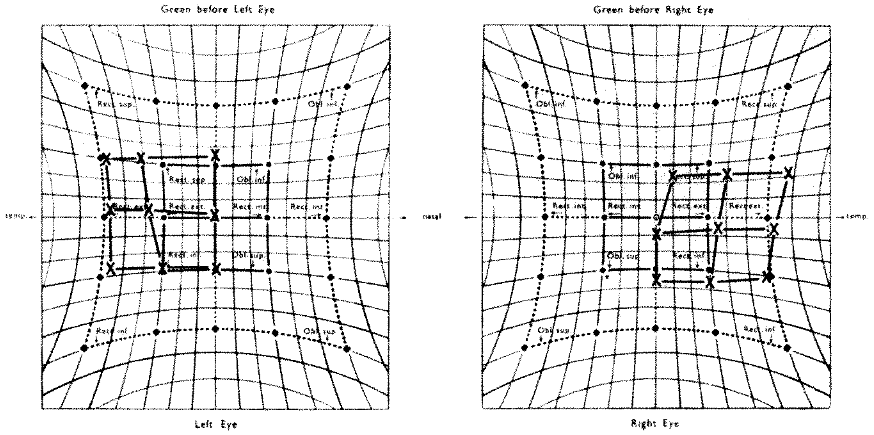

FIG. 4 *Hess charts 5 weeks later*

Result

On July 24 he had lost all diplopia and the Hess screen test was normal (Fig. 5). The patient now has full binocular vision and normal convergence to 5 in. There were no signs of any retinal or optic nerve damage and he was discharged.

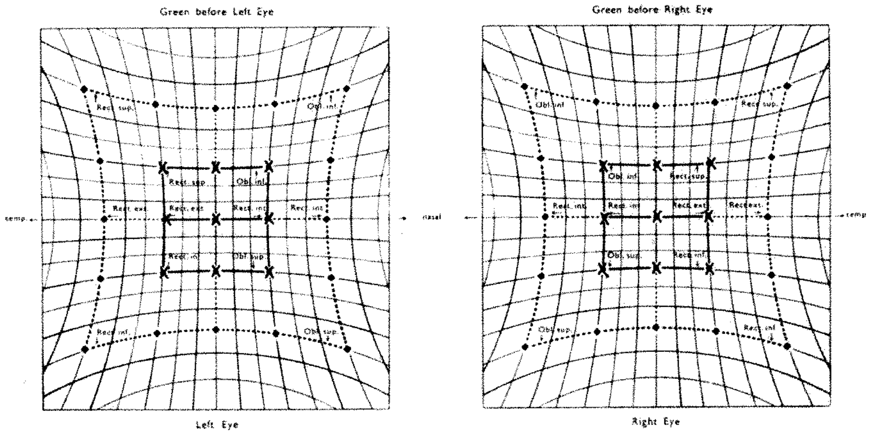

FIG. 5 *Hess charts 9 weeks after injury, showing complete recovery of binocular single vision*

Comment

This case is reported in view of the advice in the text books either to leave such a foreign body alone (Stallard, 1958), or to attempt to remove it either by a transfrontal approach or by a lateral orbitotomy (Duke-Elder, 1954).

It was felt that to leave such a large foreign body so near the apex of the orbit carried a risk of either infection or lead toxic reaction in the neighbourhood of the optic nerve.

The manipulations were carried out with extreme care and gentleness to minimise the risk of further damage and in comparison with the trauma involved by an approach either from above or from the lateral aspect, this method has much to recommend it.

It is a pleasure to record our gratitude to the Radiological Staff and to the Orthoptic Department for their painstaking help and co-operation.

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Brit. J. Ophthal. (1970) **54**, 628

Unusual type of epidemic conjunctivitis in Ghana

S. CHATTERJEE, C. O. QUARCOOPOME, AND A. APENTENG

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An unusual type of epidemic conjunctivitis swept through Ghana between June and October, 1969. The clinical features of all the cases were uniform and exhibited marked deviations from the epidemic conjunctivitis usually seen in other parts of the world. The rapid spread and course of the condition were also remarkable, and our failure to detect any of the usual causative organisms encouraged us to make closer observations. This detailed study revealed many noteworthy ophthalmological features.

General features of the epidemic

A general review of the epidemic has already been published (Chatterjee, Quarcoopome, and Apenteng, 1970).

An acute haemorrhagic conjunctivitis developed within a few hours after the initial symptom of irritation. Severe pain, marked swelling of the lids, lacrimation, and serous discharge followed. Conjunctival follicles and enlarged pre-auricular lymph glands were frequent. The disease was highly contagious and 8,981 cases were seen at the clinic in August, 1969. It had a self-limiting course of 7 to 10 days with gradual subsidence. None of the patients had corneal involvement or other complications. Conjunctival swabs were bacteriologically negative in 75 per cent. of cases. Conjunctival scraping did not show inclusion bodies (TRIC agent). Initial attempts to isolate adenovirus in the scrapings were not successful (Chatterjee and others, 1970).

Detailed analysis of subconjunctival haemorrhages

A total of 13,664 cases was seen at this clinic from June to October, 1969. From the beginning of the disease all showed subconjunctival haemorrhages associated with conjunctival inflammation. These haemorrhages, which constituted the most characteristic feature of the disease, varied from one or more minute pin-point petechia to large blotches of frank haemorrhage. The bulbar conjunctiva near the upper fornix was invariably the initial site of the lesion, which later spread to the whole of the upper half of the bulbar conjunctiva and to a variable extent to the lower fornix. Although conjunctival injection was present the haemorrhages were far more pronounced and did not correspond to the severity of the congestion. It was remarkable that no relationship could be detected between the amount of haemorrhage and the degree of chemosis or lid oedema. Indeed, some cases had the appearance of a traumatic subconjunctival haemorrhage with conjunctival congestion. One would have thought that the haemorrhages were due to rubbing the eyes because of the initial foreign body sensation, but the haemorrhage continued to increase during the first 48 hours or so. From the 5th day resorption began, and complete absorption took place in the majority of cases by the 7th to 10th day. This speedy absorption of the haemorrhage was unexpectedly rapid.

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Address for reprints: C. O. Quarcoopome, Department of Ophthalmology, Ghana Medical School, Korle Bu, Accra, Ghana

Other clinical features

These were studied in detail in 250 cases, 178 of which were examined within 24 hours of onset and the rest within 48 hours. All were new cases. People of all ages and both sexes were affected, the youngest being a week-old baby. The results are set out in Table I.

Table I *Clinical features in 250 cases of conjunctivitis*

Clinical features	*Incidence of positive findings*	
	No.	*Per cent.*
(1) Hyperaemia/congestion of upper fornix/upper half of bulbar conjunctiva with or without inflammation of lower fornix	250	100
(2) (*i*) A few minute petechiae near upper fornix only (in some cases only one or two pinpoint petechiae were noted) (*ii*) Gross haemorrhages in upper half of bulbar conjunctiva (*iii*) Haemorrhage extending to lower fornix	46 189 15	18 75 6
(3) Follicles on lower palpebral conjunctiva	153	61
(4) Enlarged pre-auricular lymph glands (one painful)	156	64
(5) Uniocular affection (six returned later with both eyes involved; nine did not return)	15	6
(6) Corneal involvement	—	—
(7) Pharyngitis	—	—
(8) Fever (history)	—	—
(9) Serous discharge	192	76
(10) Mucopurulent discharge	58	23

Laboratory investigations

Certain cases were selected from the above for aetiological investigations (Table II).

Table II *Results of aetiological investigations in selected patients*

Investigation	*No. of cases examined*	*Result*
(1) Conjunctival swab culture on blood agar and chocolate agar	57	40 no growth 17 *Staph. pyogenes* 3 *B. coli*
(2) Conjunctival swab for microscopical examination	14	Preponderance of necrotic epithelial cells with polymorphs and mononuclear cells
(3) Everted upper lid to take conjunctival scraping for microscopical examination (a few follicles were noted in each patient at the two corners of the everted lid)	12	No inclusion body (TRIC virus) found
(4) (*i*) Conjunctival scraping for viral culture on human amnion (*ii*) Conjunctival swabs for viral culture on chick embryo (*iii*) Conjunctival scrapings for viral culture on other various cell lines (HeLa cells and monkey kidney cells)	8 15 19	No growth or cytopathy detected No growth or cytopathy detected No positive result
(5) Complement-fixation test with stock group antigen of known varieties of adenovirus against acute serum and 3 weeks' convalescent serum	16	None convincingly positive in any significant dilution or in increasing titre
(6) Direct inoculation of discharge on to rabbit conjunctiva	2	No result in 4 weeks

Discussion

The main variation from usual types of epidemic conjunctivitis was the presence of sub-conjunctival haemorrhage in all cases. "Epidemic haemorrhagic conjunctivitis" would therefore be an appropriate name for this condition. An epidemic of such a predominantly haemorrhagic conjunctivitis has not, to our knowledge, been reported before.

Haemorrhage can occur in any case of severe inflammation, especially in purulent and mucopurulent conjunctivitis due to pneumococcus and haemophilus infections (Duke-Elder, 1964; Lyle, Cross, and Cook, 1968), but in our cases the discharge was serous and these pathogenic organisms could not be grown in cultures on blood or chocolate agar in

70 per cent. of cases (Table I, 9 and 10; Table II, 1). This result was convincing enough to exclude a bacterial origin. 30 per cent. of cases grew *Staphylococcus pyogenes*, but we considered this to be a secondary infection.

Absence of pharyngitis and fever (Table I, 7 and 8) and absence of TRIC virus from conjunctival scrapings (Table II, 3) differentiated the condition from trachoma, inclusion conjunctivitis, pharyngo-conjunctival fever, and Béal's conjunctivitis.

A virus is known to be capable of producing inflammation of the haemorrhagic type as in epidemic haemorrhagic fevers (Adams and Maegraith, 1966) and haemorrhagic smallpox (Nelson, 1964). Conjunctival haemorrhages have also been found in epidemic kerato-conjunctivitis, caused by an adenovirus (Hogan, 1957; Allen, 1966). Ormsby, Fowle, and Doane (1957) found two isolated cases of acute follicular conjunctivitis with subconjunctival haemorrhage in Toronto in 1954. They also noted that pseudomembrane and subconjunctival haemorrhage were frequently found in cases of epidemic kerato-conjunctivitis without corneal opacity. These facts brought us back to the idea that the present epidemic could have been due to a virus infection. Moreover, two of our patients returned with typical punctate keratitis during the follow-up period (4 months).

We were, however, unable to detect a virus in the swabs and scrapings (Table II, 4 and 5). No cytopathological changes were detected in any of the cultures attempted. Complement-fixation tests by stock adenovirus antigens with serum from acute cases and also after 3 weeks' convalescence produced no evidence of adenovirus infection. The inoculation of rabbit eyes also failed to produce any inflammation (Table II, 6).

The clinical features strongly suggested that the epidemic was caused by a variant of an adenovirus of epidemic kerato-conjunctivitis, which produced subconjunctival haemorrhage instead of corneal involvement; the epidemic spread, follicle formation, preauricular lymphadenopathy, and serous type of discharge are typical of adenovirus infections, but there was no fever or pharyngitis.

Conclusions and summary

In a large epidemic of a haemorrhagic conjunctivitis which swept over Ghana from June to October, 1969, the presence of subconjunctival haemorrhages in all cases and the absence of corneal involvement, fever, and pharyngitis were unusual features. Bacterial infection was excluded and the known strains of adenovirus could not be detected.

We wish to thank Prof. C. O. Easmon, F.R.C.S., Dean of the Ghana Medical School, for his help and support and for permission to publish this article. We are also indebted to Prof. Minami, Visiting Professor of Virology from Japan, to the Virology Department of Ghana Medical School, and to Dr. H. S. Sodhi and Dr. Djordjevic for their help in the bacteriological studies.

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Brit. J. Ophthal. (1970) **54,** 631

Malignant melanoma of the conjunctiva

AMRESH CHOPDAR

West of England Eye Infirmary, Exeter

Case report

A 65-year-old woman presented at the Outpatients Department of the West of England Eye Infirmary on January 8, 1970, complaining of a pigmented mass at the corneo-scleral junction of the right eye of uncertain duration. On questioning she remembered having previously had a small brownish spot at about 4 to 5 mm. away from the limbus.

In the past she had had some degree of hyperthyroidism and hypertension, but was free from symptoms and not receiving any treatment.

Examination

There was an elliptical pigmented lesion 6 × 3 mm. and raised by approximately 1 mm. from the surface at the temporal side of the limbus of the right eye. The lesion extended over the surface of the cornea, almost reaching to the outer margin of the pupil; there was also a slight extension laterally from the limbus to the bulbar conjunctiva. A large blood vessel was feeding the tumour from the lateral canthus (Fig. 1).

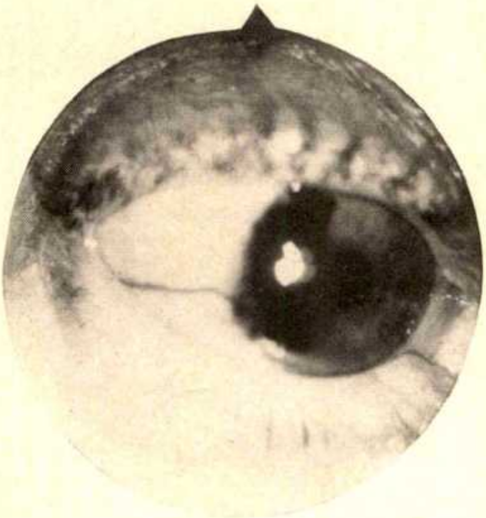

FIG. 1 *Malignant melanoma at the limbus in the right eye. Note large feeding vessel*

The visual acuity was 6/6 in the right eye, with +2·5 D sph., +0·25 D cyl., axis 90°, and 6/4 in the left eye, with +2·25 D sph., +0·25 D cyl., axis 180°.

Biomicroscopy showed a heavily pigmented mass at the limbus extending over the cornea and conjunctiva. Gonioscopy revealed wide open angles and no deposit of pigment. Ophthalmoscopy showed no abnormality.

She was admitted to hospital, where a detailed physical examination revealed no evidence of any secondary infiltration. There were no glandular swellings, no enlargement of liver or spleen, and no pigmented lesions of the skin.

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Address for reprints: Dr. Amresh Chopdar, The Royal Eye Hospital, St. George's Circus, London, S.E.1

Laboratory investigations

A peripheral blood film and liver function tests were all within normal limits.

Chest *x* ray showed no other abnormalities except a moderate dilatation of the left ventricle.

Urine melanogen was positive preoperatively and became negative postoperatively.

Treatment

A wide excision of the mass was undertaken under general anaesthesia. The large feeding vessel was cauterized first. Next a wider area of conjunctiva was excised by means of a diathermy needle. The part attached to the cornea was separated with a Castroviejo razor-blade knife and a good cleavage line was obtained. The tumour was removed completely with little difficulty. It was not necessary to remove the corneal tissue deeper than the epithelium. The bare excised area was covered by a conjunctival flap.

Histopathology report

Malignant melanoma of spindle cell type with numerous melanophages (Figs 2 and 3).

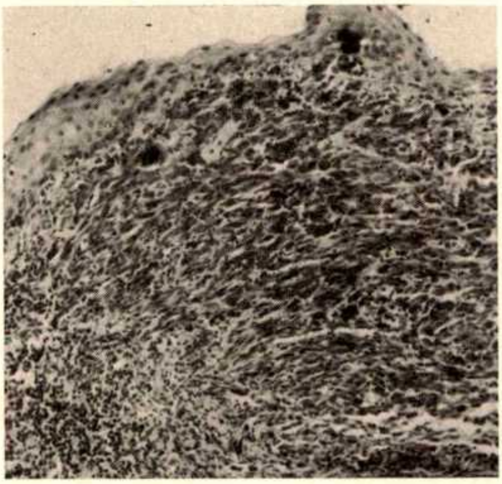

FIG. 2 *Section of excised melanoma showing spindle cells* ×7·5

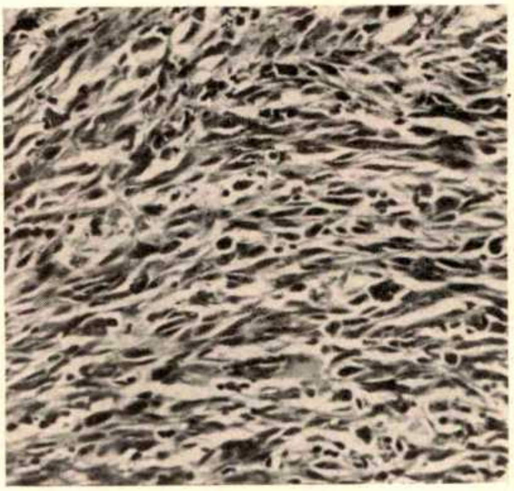

FIG. 3 *Higher magnification showing spindle cells* ×30

Radiotherapy

It was decided that she ought to have low voltage therapy of 50 kv; a total dose of 3500 r in 9 days was given to the excision area of the right eye.

Result

The patient is now completely free from symptoms and the urine melanogen is negative.

Discussion

Benign naevi are not uncommonly seen in the conjunctival sac, whereas malignant melanomata of the conjunctiva, especially the spindle cell type, are infrequent (Hogan and Zimmerman, 1962; Reese, 1963; Jay, 1964, 1965).

In this case it seems that a benign naevus had later undergone malignant change. This leads to the question whether all conjunctival naevi should be excised routinely at an early stage.

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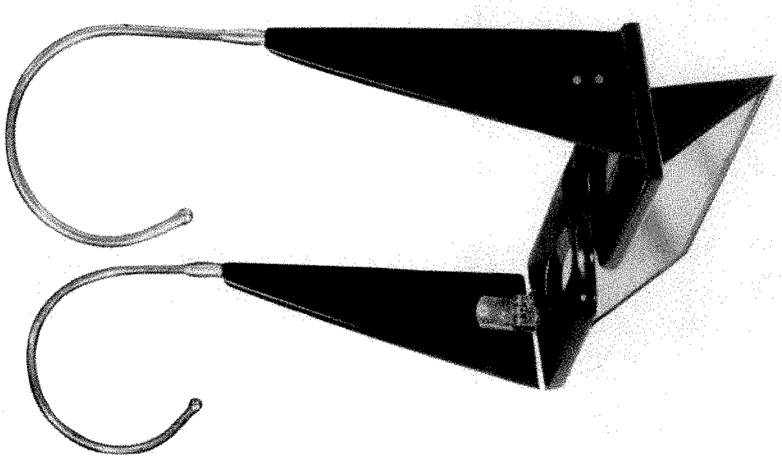

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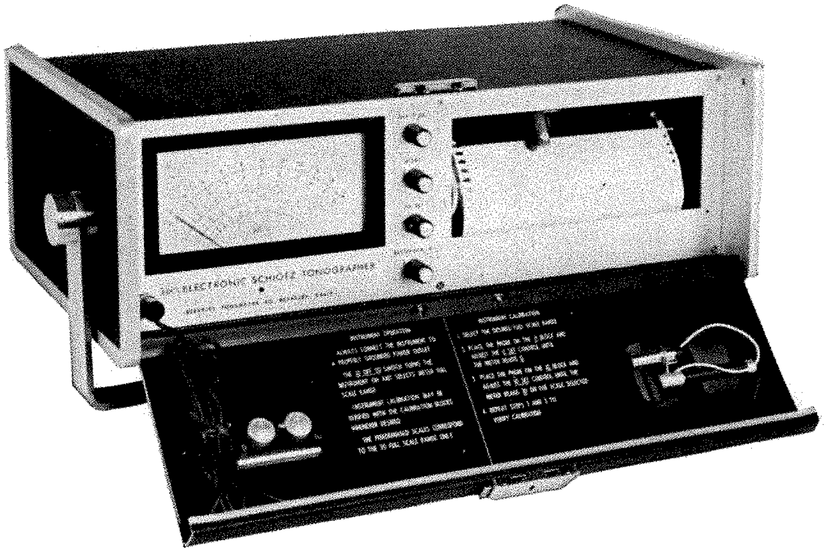

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Summary

A case of conjunctival malignant melanoma in a woman aged 65 years with positive urine melanogen was treated by means of wide excision and low voltage radiotherapy. The urine melanogen became negative after treatment.

My thanks are due to Mr. G. L. Cantrell, consultant ophthalmologist, and to Dr. R. A. Caldwell, consultant histopathologist, for their help.

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Compressed air injury of the eye

R. HITCHINGS AND J. I. McGILL
Western Ophthalmic Hospital, London

Compressed air is commonly used in industry and injuries from it are frequent, but an extensive survey of the literature revealed no reports of injury to the eye caused by compressed air alone. Such a case is reported below and the various principles involved in its treatment are discussed.

Case report

A 29-year-old engineer fell over a compressed air hose he was carrying, with the result that a high-pressure air stream, at 80 lb. per square inch, was directed towards his left eye from a range of a few inches. He was brought to the hospital 20 minutes later.

Examination

The visual acuity was 6/9 in both eyes. There was surgical emphysema of the lid and conjunctiva of the left eye, closing the palpebral fissure (Fig. 1). No entry wound in either the conjunctiva or the eye was seen, nor was there any evidence of ocular injury. Ocular movements were restricted, principally those of abduction and elevation in the left eye, resulting in diplopia in all positions of gaze. The Hess chart showed no localized muscle weakness.

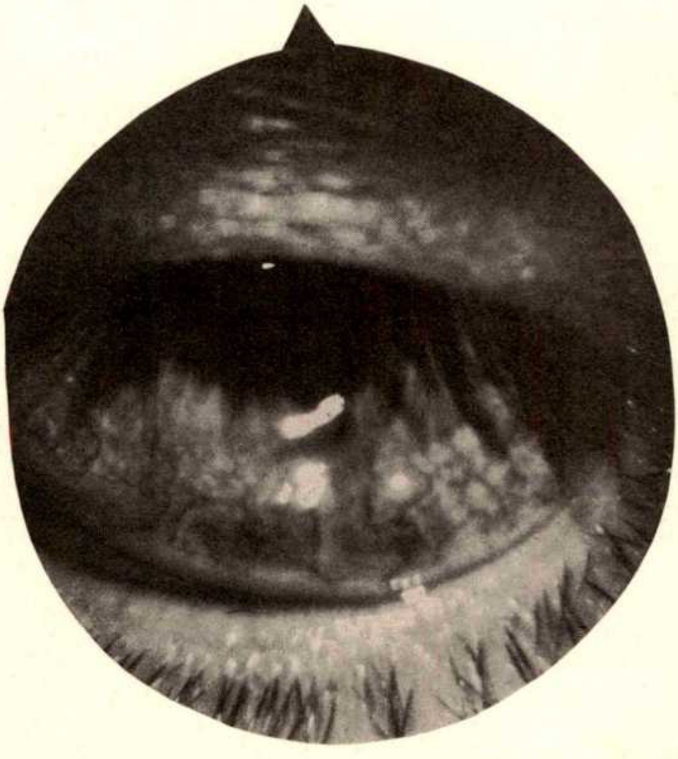

FIG. 1 *Appearance of injured eye at first examination*

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Address for reprints: Moorfields Eye Hospital, City Road, London, E.C.1

X ray showed delineation of the globe by air (Fig. 2), but tomograms showed no ethmoid fracture or blow-out fracture of the orbital floor.

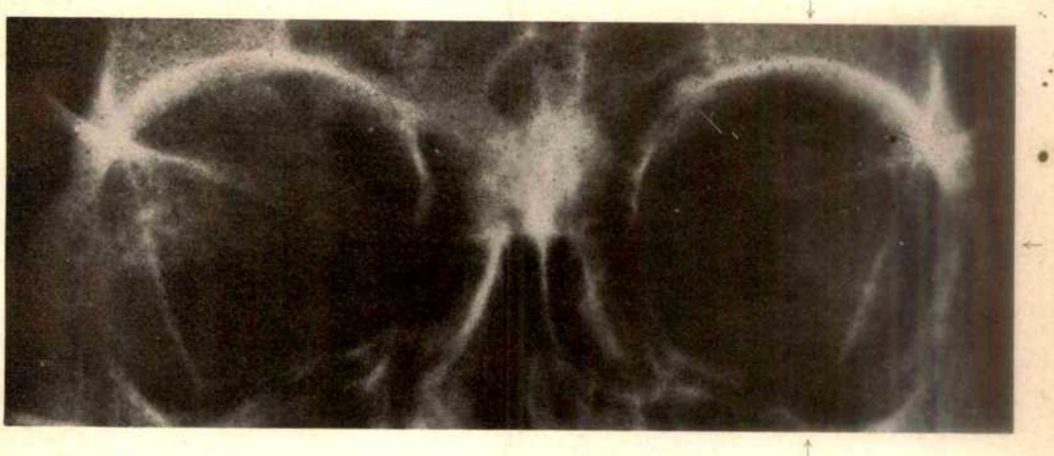

FIG. 2 *Radiograph of orbits, showing the left globe surrounded by air (arrows)*

Treatment

He was given systemic and topical antibiotics, and within 4 weeks the diplopia and emphysema had resolved completely.

Discussion

In every case of orbital emphysema associated with trauma, a fracture of the ethmoid bone should be considered. In this case it seems that the emphysema was due primarily to the high-pressure jet of air and not to a blow-out fracture of the orbital floor or a fracture of the ethmoid bone.

No entry wound was discovered, but the extremely tight apposition of the lids to the globe precluded detection of conjunctival rupture in the fornices.

Any high-pressure injury to the orbit can be dangerous in several ways:

(1) Contusion injury to the orbital contents;

(2) Intraocular or intraorbital foreign body;

(3) Inflammation secondary to infection or to a retained foreign body (*e.g.* grease-gun injury—Dallas, 1968);

(4) A jet of air could cause a displacement of the orbital contents, with either a blow-out fracture or a forward protrusion of the globe;

(5) The intraorbital air may enter the cranial cavity by the way of the optic nerve sheath or through a fracture of the orbital wall (Tenner and Trokel, 1968).

This case illustrates yet another industrial hazard, highlighting the necessity for correct ocular protection; it provides a useful reminder of the possible ocular risks involved in handling seemingly innocuous tools.

We are grateful to Mr. R. A. Burn for permission to publish this case.

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Brit. J. Ophthal. (1970) **54**, 636

Correspondence

Orbital rhabdomyosarcoma

To the Editorial Committee of the **British Journal of Ophthalmology**

SIRS,—Concerning the article, "Orbital Rhabdomyosarcoma in an Infant" by G. C. Sood, D. K. Sen, R. Diwan, and A. L. Aurora (*British Journal of Ophthalmology*, 1970, **54**, 203), I should like to bring to your attention our recent publications concerning the role of radiation therapy in the management of this disease. It is apparent that our experience differs from that of Dr. Lederman and it is our belief that radiation therapy should become the treatment of choice in this disease. The reasons for our differing experience remain obscure. I can add that current evaluation of the originally reported patients, and subsequent experience, serve only to confirm our impression.

Yours faithfully,

ROBERT H. SAGERMAN

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May 19, 1970

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Book reviews

Ophthalmic Genetics. By A. SORSBY. 2nd ed., 1970. Pp. 269, 235 figs, bibl. Butterworth, London. (110*s*.)

This second edition of Prof. Arnold Sorsby's "Genetics in Ophthalmology", originally published in 1951, has been almost completely rewritten and can be considered a new book on this subject. It is arranged in three sections: the globe as a whole, individual tissues, and generalized disorders with ocular aspects.

This is a concise and eminently readable textbook of ophthalmic genetics and as such is unequalled. There are several typographical errors in the text, certain of the terminology is old-fashioned or even incorrect (choroidal sarcoma, p. 5), and a few statements are confusing, controversial, or inaccurate. Retinal aplasia is used as the name for a specific entity (Alström and Olson) and also for certain of the atypical forms of retinitis pigmentosa; this is confusing. Haldane's interpretation of dominant partial sex-linkage for a family with retinitis pigmentosa hardly merits mention; transmission appears to be autosomal dominant. Ichthyosis is said generally to be recessive, yet autosomal dominant transmission is the most common with autosomal recessive transmission being distinctly uncommon. Despite these minor criticisms this book can be recommended to all ophthalmologists as an excellent readable manual on this important subject.

Manual of Refraction. By A. E. SLOANE. 2nd ed., 1970. Pp. 282, 54 figs, bibl. Little Brown, Boston; Churchill, London. (110*s*.)

This second edition of the "Outlines of Refraction" is similar in form to the first, but new chapters on streak retinoscopy and recent trends in refraction have been added. The book, based on lecture notes in refraction given to post-graduate students, sustains its original elementary approach to the problems of refraction which it presents in a clinical form. The optical principles underlying the practice of refraction are not dealt with in great depth and only a very small amount of mathematics is displayed.

The book is easily and quickly read and may serve to augment clinical aspects of refraction not covered fully by more comprehensive text-books, although the expense probably will outweigh these debatable advantages.

Ultrasonography in Ophthalmology. By J. VANÝSEK, J. PREISOVÁ, and J. OBRAZ. 1970. Pp. 222, 100 figs, bibl. Czechoslovak Medical Press, Prague; Butterworths, London. (76*s*.)

This is a review of 8 years' experience of a group of pioneers in this new field. The first part of the book is devoted to the physical properties of ultrasound and the instrumentation for its use in ophthalmology. The average clinician will be flattered by the authors' assumption that this will be readily intelligible to him, but it does at least emphasize that there is more to the subject than mere bat-squeak echography.

The clinical section occupies half the book, but it is expanded by case histories and illustrations of echograms so that the amount of clinical material is less than may be apparent at first sight. It is apparent that most of the work has been carried out by the A-scan method. Emphasis is placed on the investigation of ocular tumours, retinal detachment, intra-ocular foreign bodies, and ocular measurement. There is a section on the more difficult technique of studying orbital lesions.

Ultrasonography is a very new technique but its potentials in some fields, as in eyes with opaque media, have always been obvious, In most of the cases cited by the authors it would seem that the investigation offered little more information than could be obtained by well-established methods. A feature of note is the possibility of relating a foreign body to the walls of the globe, thus showing whether it is extra- or intra-ocular. More diagnostic accuracy may be expected, although the authors have added a note of caution in that ultrasound is potentially damaging to tissues. A theoretical possibility of great potential is that the nature of a tissue may be predicted from its reflecting properties to various wavelengths of ultrasound.

The Vitreous in Clinical Ophthalmology. By N. S. JAFFE. 1969. Pp. 310, 334 figs (some col.), bibl. Mosby, St Louis; Kimpton, London. (292*s*.)

This book is written by a clinician seeking to explain clinical observations by applying factual knowledge and hypotheses to the behaviour of a tissue about which little was known before the introduction of the newer methods of examination. The author is to be congratulated on gathering an extensive bibliography dealing with current concepts of the normal vitreous, the part it plays in producing complications after lens extraction, and its role in retinal detachment, diabetic retinopathy, and many of the more rare clinical syndromes. Most of the hypotheses are supported by credible logic, but there are occasional lapses into such emotive statements as "the inadequate surgeon does not belong in the operating room. He should restrict his manipulations to the intact globe".

A suitable proportion of the text is devoted to a detailed description of surgical techniques.

The book is well illustrated and is thoroughly recommended as a book of reference for clinical problems related to the vitreous.

Facial Injuries. By R. C. SCHULTZ. 1970. Pp. 264, 174 figs. Year Book Medical Publishers, Chicago; Wiley, Chichester. (136*s*.)

A well-illustrated, well-produced book, but one which is not intended for ophthalmic surgeons. Indeed the ocular signs, where relevant, are poorly described.

Notes

Ophthalmological Society of the United Kingdom

90*th Annual Congress, April* 1970

The 90th Annual Congress of the Ophthalmological Society of the United Kingdom, held at Churchill College, Cambridge, on April 6–8, 1970, under the presidency of Mr. T. Keith Lyle, departed from the pattern of its predecessors. There were some sixteen "free papers" and two symposia, but there was also an afternoon of seminars.

These seminars, twelve in number, had a chairman and three panellists, and up to 25 members of the Congress could attend each seminar which lasted 1¼ hours. There were thus two sessions in the afternoon separated by a tea interval. The subjects included "Management of palsy of traumatic origin", "Simple glaucoma", "Modern techniques in retinal detachment", "Pallor of the disc", "Herpes simplex", "Iatrogenic ocular disease", "Recent trends in prosthetics, implants, and contact lenses", "Retinal vascular disease", "Retinal neoplasm", "Recent trends in corneal transplantation", "Complicated lacrimal obstruction", and "Modern therapy of uveitis". The layout at Churchill College was ideal for this type of session which seemed very popular with the members, but it seems unlikely that this could be repeated at the Royal College of Physicians, London, as the required number of rooms would not be available. Though, because of the time taken up by the symposia and seminars, there were only sixteen "free papers", these were all of a high standard introducing new ideas.

Mr. J. C. Mustardé discussed the surgical approach to tumours of the eyelid. He emphasized that the upper lid should not be used to make up defects of the lower lid. He described a method of reconstructing the lower lid by rotation of a cheek flap lined with a composite graft of nasal septal mucosa and cartilage, and of reconstructing the upper lid by using a switch flap taken from the lower lid.

Dr. Charles D. Kelman flew from New York to read his paper on "Phaco-emulsification"; a film showing this technique was accompanied by his own music! In this technique the lens matter is aspirated through a 2-mm. incision at the limbus. A high-frequency needle surrounded by a protective silicon sleeve emulsifies the lens matter which is removed by suction with a flow of fluid.

Mr. J. D. Scott discussed retinal detachment surgery without drainage of fluid. Using silastic sponge plombage, he advocates that the implant should be radial to the limbus rather than circumferential, to avoid the danger of that the retinal hole will gape.

Mr. R. F. Fisher showed that there is a relationship between lens fibre stress, as in accommodation, and lens opacity formation.

About 100 cases of meningomyelocele with and without hydrocephalus were reviewed by Mr. D. B. Clements and Mr. K. Kaushal. Though 75 per cent. of the patients with hydrocephalus had squints, usually convergent due to lateral rectus weakness, the prognosis for binocular functions is good with early treatment, though a number correct spontaneously with alleviation of the primary condition.

The possibility of preventing primary angle-closure glaucoma was discussed by Dr. R. F. Lowe.

The first symposium on "Ophthalmic conditions associated with genetic disorders" dealt with some inborn errors of metabolism, fundus dystrophies, ocular myopathy, and the multifactorial inheritance of "simple" glaucoma.

The second symposium on "Orbital disease" was arranged by Prof. Barrie Jones and the Staff of the Orbital Clinic, Moorfields Eye Hospital. The use of contrast media and other special methods of examination to reach a clinical diagnosis of proptosis were discussed. Mr. P. Fells stated that the study of thyroid autoantibodies, including thyroglobulin, second colloid antibody, and microsomal C.F.A., was the most important test for endocrine exophthalmos. Prof. Barrie Jones described a new surgical approach to the orbit—the extended lateral approach—in which an osteo-muscular flap from an osteotomy just in front of the temporo-mandibular joint is swung out to expose the whole orbit.

Once again Exhibitors displayed the whole range of new and old ophthalmic instruments, and this year there was a show of optico-kinetic nystagmus instruments by Mr. I. D. C. Pain.

European Ophthalmic Pathology Society

IX Annual Meeting, May, 1970

The European Ophthalmic Pathology Society held its ninth annual meeting at the Europa Hotel, Ghent, Belgium, on May 28 to 30, 1970. Dr. F. C. Blodi (*Iowa City, U.S.A.*) and Prof. J. François (*Ghent*) were the guests of honour. Dr. M. Hanssens, assisted by Mrs Hanssens, organized the scientific and social programme, which began with a reception at the hotel and a dinner at the home of Prof. and Mme François. The annual dinner was held at Laarne Castle, and the meeting concluded with a visit to Brussels where an informal dinner was held at *La Chaloupe d'Or*.

The meeting was attended by 31 members:

Prof. J. Casanovas, President (*Spain*)
Prof. N. Ashton, Life President (*Gt. Britain*)
Dr. S. Ry Andersen (*Denmark*)
Prof. K. Arneson (*Norway*)
Prof. H. Babel (*Switzerland*)
Dr. R. Barry (*Gt. Britain*)
Prof. P. Bec (*France*)
Dr. B. A. Bembridge (*Gt. Britain*)
Prof. J. Bock (*Austria*)
Dr. Alfred Brini (*France*)
Prof. P. Danis (*Belgium*)
Dr. P. Dhermy (*France*)
Prof. H. Fanta (*Austria*)
Prof. G. Günther (*E. Germany*)
Dr. A. Garner (*Gt. Britain*)
Prof. A. Hagedoorn (*Holland*)
Dr. A. Hamburg (*Holland*)
Dr. M. Hanssens (*Belgium*)
Dr. O. A. Jensen (*Denmark*)
Dr. E. Kock (*Sweden*)
Dr. E. Landolt (*Switzerland*)
Prof. Olga Litricin (*Jugoslavia*)
Prof. O-E. Lund (*W. Germany*)
Dr. W. A. Manschot (*Holland*)
Dr. G. Morgan (*Gt. Britain*)
Dr. Joan Mullaney (*Ireland*)
Dr. G. Naumann (*W. Germany*)
Prof. A. Nover (*W. Germany*)
Dr. G. Scuderi (*Italy*)
Prof. R. Seitz (*W. Germany*)
Prof. A. H. A. Tarkkanen (*Finland*)

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Invited guests were Dr. E. Balestrazzi (*Italy*) and Prof. M. Brihaye-van Geertruyden (*Belgium*).

The next (10th) meeting will be a Joint Meeting with the American Verhoeff Society which is celebrating its 25th anniversary, and will be held in London on April 25 to 28, 1971, when Prof. N. Ashton will act as organizing secretary.

Faculty of Ophthalmologists

Officers, 1970–71

At the Council meeting on June 12, 1970, the following were elected:

President:	Mr. A. G. Cross
Immediate Past President:	Mr. T. Keith Lyle
Vice-Presidents:	Mr. A. G. Palin Mr. J. R. Hudson
Hon. Treasurer:	Mr. E. C. Zorab
Hon. Secretary:	Mr. L. G. Fison

Symposium on Disorders of Ocular Motility

Moorfields Eye Hospital, November 13 and 14, 1970

A Symposium for consultant ophthalmologists will be held in the Ocular Motility Clinics of Moorfields Eye Hospital on Friday November 13 and Saturday morning November 14, 1970. There will be lectures, panel discussions, and patient demonstrations.

The registration fee of 7 guineas includes dinner on Friday evening and luncheon on Friday and Saturday.

Applications to attend should be sent to The Director, Orthoptic Department, Moorfields Eye Hospital, High Holborn, London, W.C.1. Numbers are limited and early application is recommended.

Symposium on Retinal Surgery

Moorfields Eye Hospital, November 26 to 28, 1970

The Retinal Unit, Moorfields Eye Hospital, City Road, will hold a symposium for consultants on the Diagnosis, Treatment, and Complications of Retinal Detachment and Allied Conditions at the Moorfields Annexe, Highgate, from Thursday, 26 November, at 7 p.m., to Saturday, 28 November, at 3 p.m. Cases will be shown and the techniques used in this Unit will be demonstrated. Controversial aspects of this subject will be discussed at a Panel Discussion at Kenwood House.

The registration fee of 8 guineas includes dinner on Thursday and Friday. Cars will leave the President Hotel, Russell Square, W.C.1, after breakfast on Friday and Saturday mornings.

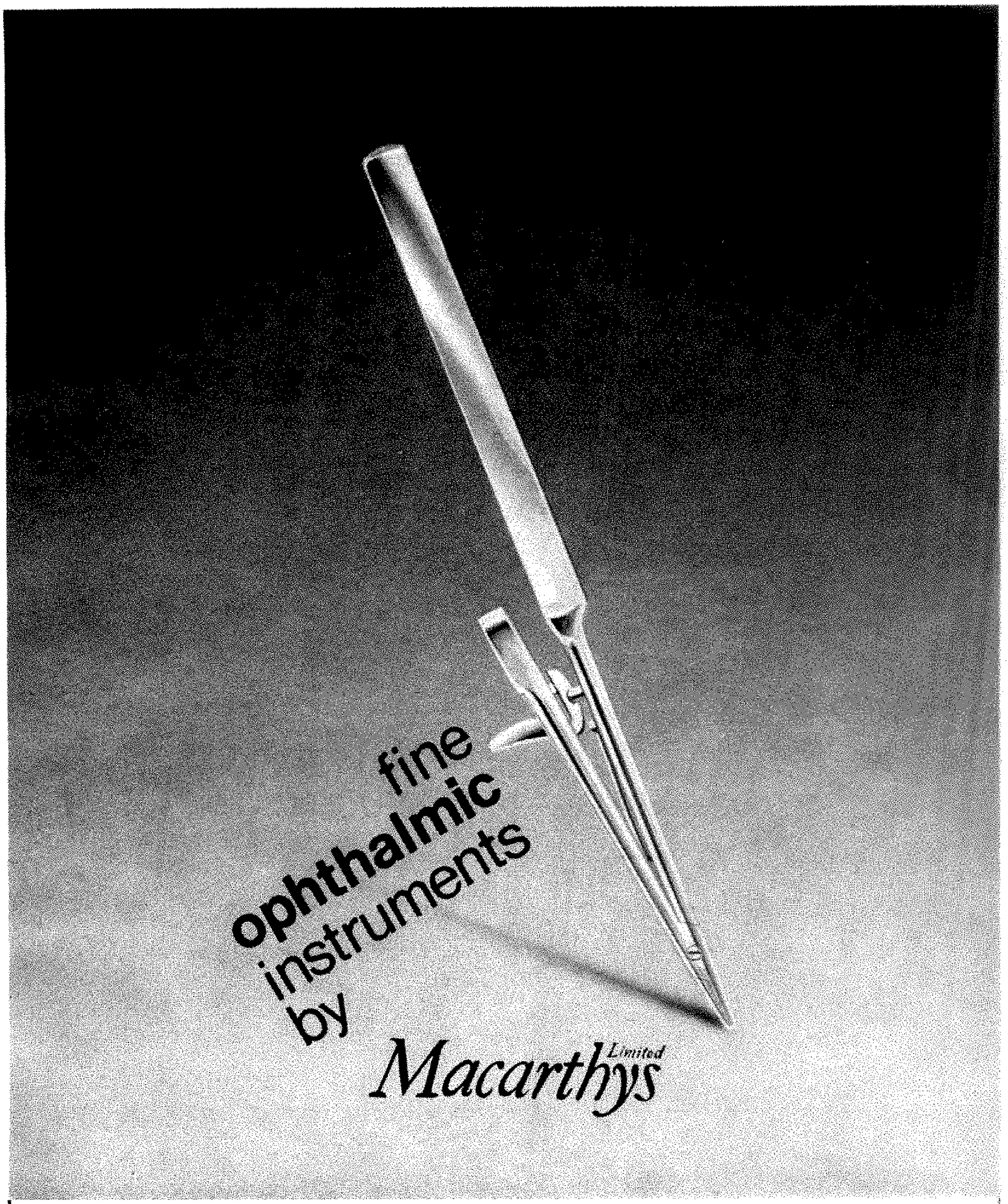
Applications to attend should be sent to Mr. Lorimer Fison, 104 Harley Street, W.1, by October 1, 1970. Numbers are limited by the space available at the Highgate Annexe and early application is recommended.

Iris Clip Lens and Irido-Capsular Lens Techniques

Training Course, Terneuzen, May, 1971

A special course with a clinical and surgical programme on lens implants with fixation to the iris will be held from May 17 to 21, 1971, at Terneuzen (Netherlands). Participation will be strictly limited to eye surgeons with a thorough surgical background and all applications should be supported by the head of a well-known eye department.

Please apply before October, 1 1970, to Dr. C. D. Binkhorst, Axelsestraat 54, Terneuzen, The Netherlands.



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For particulars apply to the Director of the Department of Pathology.

LISTER RESEARCH FELLOWSHIP 1971

The Lister Research Fellowship will become vacant on 1st, January 1971

It is given to the nationals of any country for research at the Institute of Ophthalmology and Moorfields Eye Hospital for a year, with the possibility of extension for a further year. The annual salary is £1,700 (sterling) plus a living allowance of £800 (total £2,500 p.a.).

Application forms and further particulars are obtainable from the House Governor, Moorfields Eye Hospital, City Road, London E.C.1. to whom applications should be returned by 1st, November 1970.

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TELEVISION OPHTHALMOSCOPY: Instrumentation and Medical Applications *by* **Richard L. Dallow,** *Dept. of Health, Education and Welfare, Washington. Foreword by* **Cesar A. Caceres.** Brings together information and background material for an understanding of basic aspects of the system. This material includes anatomy of the eye, methods of documenting the ocular fundus, principles of television picture production, techniques of image enhancement for special effects, individual components and the system as a whole, and technical problems of operation. '70, 120 *pp.* (6¾ × 9¾), 42 *il.*, 1 *table*, $8.50.

CONTACT LENS MEDICAL SEMINAR: Volume I. *Proceedings of the First Biennial Contact Lens Medical Seminar Held in Conjunction with the Annual Meeting of the American Academy of Ophthalmology and Otolaryngology edited by* **Whitney G. Sampson** *and* **Gerald L. Feldman.** *Foreword by* **Joseph M. Dixon.** *Introduction by* **Abraham Schlossman.** (10 *Contributors*) Covers fundamentals as well as clinical applications of corneal physiology, control and management of optical problems, selected fitting problems, and scleral lenses. Major emphasis is on simplicity and ease of adapting basic procedures to office practice. '70, 192 *pp.*, 31 *il.*, 17 *tables*, $10.50.

EYE INJURIES *by* **Edward Zagora,** *Univ. of Sherbrooke, Canada.* Incidence, etiology, pathology, diagnosis, prognosis, prophylaxis, and treatment for most conditions are discussed. Chapters on post-traumatic plastic surgery are presented. Ocular symptoms associated with neurological and neurosurgical conditions due to trauma are included. Clinical photographs, fundus photographs, drawings, diagrams, and tables supply abundant illustrative material to supplement the text. Deals with every aspect of medical and surgical treatment of eye injuries. '70, *about* 732 *pp.* (7 × 10), 375 *il.* (7 *in full color*), 4 *tables.*

SPECTACLES FOR APHAKIA *by* **Curtis D. Benton, Jr.,** *Broward General Hosp., Fort Lauderdale, Florida, and* **Robert C. Welsh,** *Univ. of Miami.* '66, 176 pp. (6¾ × 9¾), 96 il., 11 tables, $8.75

NEUROLOGY OF THE OCULAR MUSCLES (2nd Ed., 5th Ptg.) *by* **David G. Cogan,** *Harvard Med. School, Boston.* '70, 320 pp., 169 il. (3 in full color), $10.50

NEUROLOGY OF THE VISUAL SYSTEM (4th Ptg.) *by* **David G. Cogan.** '70, 432 pp., 180 il. (3 in full color), $14.50

COLOR BLINDNESS: An Evolutionary Approach *by* **Ricardo Cruz-Coke,** *Univ. of Chile, Santiago.* '70, about 166 pp., 57 il., 24 tables

REHABILITATION COUNSELING OF THE BLIND *by* **Thomas A. Routh,** *Hospital and Welfare Board, Tampa, Florida.* '70, 100 pp., $6.75

FUNDAMENTALS OF VISUAL SCIENCE *by* **Melvin L. Rubin,** *Univ. of Florida College of Medicine, Gainesville; and* **Gordon L. Walls,** *Univ. of California School of Optometry, Berkeley. Foreword by* **James E. Lebensohn.** '69, 460 pp., 85 il., 4 tables, $17.50

SO YOU HAVE CATARACTS: What You and Your Family Should Know *by* **Albert E. Sloane,** *Harvard Medical School, Boston, Massachusetts.* '70, about 200 pp., 5 il.

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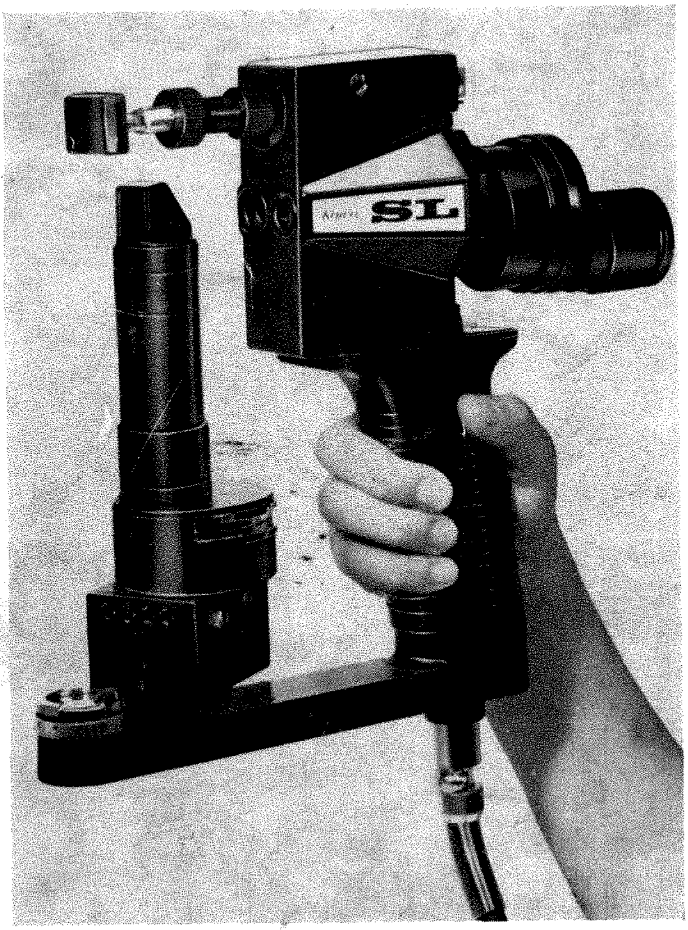

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